CLINICAL PROTOCOL

AN OPEN-LABEL TRIAL TO ADDRESS THE SAFETY OF THE SMARTFLOW MR-COMPATIBLE VENTRICULAR CANNULA FOR ADMINISTERING ELADOCAGENE EXUPARVOVEC TO PEDIATRIC SUBJECTS

PTC-AADC-GT-002

01 SEPTEMBER 2023

VERSION 11.0

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The eSignature page is located on the last page.

PRINCIPAL INVESTIGATOR AGREEMENT AND SIGNATURE

I have read the protocol document and, on behalf of my institution, agree to comply with the protocol and all applicable regulations.

Principal Investigator	**Date**

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SYNOPSIS

Name of Sponsor/Company:	PTC THERAPEUTICS, INC.
Study Number:	PTC-AADC-GT-002
Study Title:	An Open-Label Trial to Address the Safety of the SmartFlow MR-Compatible Ventricular Cannula for Administering Eladocagene Exuparvovec to Pediatric Subjects
Study Objectives:	**Primary Study Objectives** • To assess the pharmacodynamics (PD) of eladocagene exuparvovec treatment by evaluation of homovanillic acid (HVA) levels at 8 weeks after administration • To assess the safety of the SmartFlow magnetic resonance (MR)-compatible ventricular cannula for administering eladocagene exuparvovec to pediatric subjects **Secondary Study Objectives** The secondary study objectives of the study are as follows: • To assess the PD of eladocagene exuparvovec by evaluation of the following: o HVA at Week 48 o Positron emission tomography (PET) at Weeks 8 and 48 o 5-hydroxyindoleacetic acid [5-HIAA] at Weeks 8 and 48 o 3-O-methyldopa [3-OMD]) at Weeks 8 and 48 • To evaluate the long-term efficacy of eladocagene exuparvovec through Month 60 as assessed by the following: o Motor milestone attainment o Peabody Developmental Motor Scale, second edition (PDMS-2) score o Bayley Scale of Infant Development, third edition (Bayley-III) o EQ-5D-Y o Body weight o Aromatic L-amino acid decarboxylase (AADC)-specific symptoms • To evaluate the safety of eladocagene exuparvovec treatment as assessed by treatment-emergent adverse events (TEAEs), neurological examinations, magnetic resonance imaging (MRI), and clinical laboratory tests.
Phase of Trial:	Phase 2
Study Design:	This is an open-label study in subjects with AADC. Eligible pediatric subjects will receive eladocagene exuparvovec at 1.8×10^{11} vector genomes (vg) via the SmartFlow MR--compatible ventricular cannula in a single operative session. Subjects will receive standard of care for AADC deficiency during the study. This study will have a Trial Phase, an Extension Phase, and a Long-Term Extension Phase. The primary objectives of the Trial Phase are to assess the PD of eladocagene

	exuparvovec treatment by evaluation of HVA levels and to assess the safety of the SmartFlow MR-compatible- ventricular cannula for administering eladocagene exuparvovec to pediatric subjects with AADC deficiency. The secondary objectives of the Trial Phase are to further assess the PD of eladocagene exuparvovec in subjects with AADC deficiency using neurotransmitter metabolite assessment and PET analysis. The Extension Phase is designed to capture additional clinical information for eladocagene exuparvovec through study evaluations, changes in motor development, AADC-specific symptoms, and other PD measures. The Extension Phase will be complete at 48 weeks after administration of eladocagene exuparvovec. The Long-Term Extension Phase will capture long-term safety and efficacy data, for subjects treated with eladocagene exuparvovec, through Month 60. A Data Safety Monitoring Board (DSMB) will conduct a review of safety data as outlined in the DSMB charter. Review by DSMB will not be required in order to enroll successive subjects. The DSMB will monitor ongoing study results to ensure subject well-being, safety, and study integrity.
Study Population:	Pediatric subjects with AADC deficiency. At minimum, 3 subjects will be enrolled for this study.
Inclusion/ Exclusion Criteria:	**Inclusion criteria:** 1. Pediatric subjects must have genetically confirmed AADC deficiency with typical clinical characteristics and decreased AADC enzyme activity in plasma. 2. Age range from 1 year to <18 years. 3. Cranium sufficiently developed to allow placement of ClearPoint system for stereotactic surgery. 4. Persistent neurological defects secondary to AADC deficiency despite standard medical therapy (dopamine agonists, monoamine oxidase inhibitor, pyridoxine, or other forms of vitamin B6) in the opinion of the investigator. 5. Unable to ambulate independently (with or without assistive device). 6. Baseline hematology, chemistry, and coagulation values within the normal pediatric laboratory value ranges, unless in the investigator's opinion the out-of-range values are not clinically significant with respect to the subject's suitability for surgery. 7. Subject must test negative for coronavirus disease of 2019 (COVID-19) a maximum of 72 hours prior to receiving gene therapy. 8. Subject must be on stable dosage for 3 months prior to baseline for all medications related to treatment of AADC deficiency, including dopamine agonists, monoamine oxidase inhibitors, anticholinergic drugs, and vitamin B6.

	9. Females of childbearing potential must have a negative pregnancy test at screening and baseline and agree to abstinence or double-barrier form of contraception for the duration of the study following discharge from the hospital (acceptable methods will be determined by the site). 10. Males sexually active with females of childbearing potential must agree to use a barrier method of birth control during the study following discharge from the hospital. 11. Parent(s)/legal guardian(s) with custody of the subject must agree to comply with the requirements of the study, including the need for frequent and prolonged follow-up. 12. Parent(s)/legal guardian(s) with custody of the subject must give their consent for subject to enroll in the study. **Exclusion criteria:** 1. The subject has presence of other significant medical or neurological conditions that would create an unacceptable operative or anesthetic risk. 2. Subjects with pyridoxine 5'-phosphate oxidase or tetrahydrobiopterin (BH4) deficiency. 3. Contraindication for imaging studies (computed tomography [CT] scan, PET, or MRI), including sedation limitations or metal that would interfere with a brain MRI. 4. Anti-adeno-associated virus, serotype 2 (anti-AAV2) antibody titer higher than 1:1200 or >1 optical density value by enzyme-linked immunosorbent assay. 5. Subjects that have received treatment with other experimental therapies within the last 24 weeks prior to planned gene therapy administration, or any treatment ever with a gene therapy. 6. Evidence of a clinically active infection. 7. Females who are pregnant or breast feeding.
Study Treatment:	Eladocagene exuparvovec, administered 1.8×10^{11} vg during a one-time surgical procedure.
Study Endpoints and Evaluations:	**Primary Endpoints and Evaluations** • The primary efficacy endpoint is the change from baseline in HVA metabolite levels at the end of the Trial Phase (8 weeks after administration). • The primary safety endpoint is the assessment of adverse events (AEs) associated with the surgical administration of eladocagene exuparvovec to pediatric subjects using the SmartFlow MR-compatible ventricular cannula at the end of Trial Phase (8 weeks after administration).

Secondary Endpoints	The secondary endpoints are as follows: • Change from baseline in neurotransmitter cerebrospinal fluid (CSF) metabolite HVA (at 48 weeks after administration) • Change from baseline in PET imaging of putaminal-specific L-6-[^{18}F] fluoro-3,4-dihydroxyphenylalanine (^{18}F-DOPA) PET uptake at the end of the Trial Phase (8 weeks after administration) and the Extension Phase (48 weeks after administration) • Change from baseline in neurotransmitter CSF metabolites 5-HIAA and 3-OMD at 8 and 48 weeks after administration • Attainment of motor milestones • Motor development as assessed by the PDMS-2 • Cognitive and language development as assessed by Bayley-III • Change in EQ-5D-Y • Change in body weight • Assessment of AADC-specific symptoms • Overall safety profile characterized by type, frequency, severity, timing, and relationship to study treatment of any TEAEs, neurological examination findings, brain imaging, or laboratory abnormalities.
Statistical Methods:	Summaries and descriptive statistics will be provided for PD, safety, and efficacy variables from time of gene therapy administration until the end of follow-up. If needed, summaries will be provided for PD, efficacy, and safety variables at a timepoint that matches the agreement with the health authority. Observed values and change from baseline in HVA at Week 8 will be summarized using descriptive statistics (count, mean, standard deviation, median, minimum, and maximum) for each timepoint Observed values and change from baseline in the neurotransmitter CSF metabolites HVA, 5-HIAA, 3-OMD in CSF; brain ^{18}F-DOPA PET; PDMS-2 total and subscale scores; Bayley-III cognitive and total language subscale scores; EQ-5D-Y scores; body weight; and AADC-specific symptoms will be summarized using descriptive statistics (count, mean, standard deviation, median, minimum, and maximum) or proportion as appropriate for each timepoint. The number and percentage of subjects who achieve each motor milestone will be summarized by timepoint. Oculogyric crisis diary data will be summarized by severity, frequency, and proportion and duration of time subjects experienced oculogyric crises (OGC) during the study for selected timepoints, as appropriate. Respiratory infection rate will be summarized over time. The primary safety analysis will focus on TEAEs that are defined as AEs with a start date after or worsen after receiving eladocagene exuparvovec. The time of gene therapy administration will be the start time of the first infusion. All AEs reported will be coded using MedDRA. The

	number and proportion of subjects reporting TEAE will be summarized by System Organ Class (SOC) and by Preferred Term (PT) within SOC. Summaries will also be provided for each severity grade, relationship to the cannula device, to gene therapy, and to neurosurgical procedure, and for AEs of special interest. The number of subjects who experience dyskinesia, number of dyskinesia episodes, median time to first episode, and summary statistics for duration of dyskinesia events will be provided. Physical examination, vital signs, MRI, clinical laboratory values, T-cell, anti-AAV2 antibody values, and viral shedding will be summarized by visit, and shift table(s) will be provided if appropriate.

PROTOCOL IDENTIFIERS AND STUDY PERSONNEL

Project Code	PTC-AADC
Therapeutic Area	Gene therapy
PTC Therapeutics Substance Identifier	Eladocagene exuparvovec
IND Number	IND 019653
EudraCT Number	N/A
ClinicalTrials.gov Identifier	NCT04903288
Protocol Number	PTC-AADC-GT-002
Protocol Version	Version 11.0
Protocol Version Date	01 September 2023
Protocol Phase	Phase 2
Protocol Title	An Open-Label Trial to Address the Safety of the SmartFlow MR-Compatible Ventricular Cannula for Administering Eladocagene Exuparvovec to Pediatric Subjects
PTC Medical Monitor	[redacted]
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PTC Study Manager	

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialized Term	Explanation
^{18}F-DOPA	L-6-[^{18}F] fluoro-3,4-dihydroxyphenylalanine
3-OMD	3-*O*-methyldopa
5-HIAA	5-hydroxyindoleacetic acid
5-HTP	5-hydroxytryptophan
AADC	Aromatic L-amino acid decarboxylase
AADC	Aromatic L-amino acid decarboxylase (gene)
AAV2	Adeno-associated virus, serotype 2
AE	Adverse event
AESI	Adverse event of special interest
AIMS	Alberta Infant Motor Scale
aPTT	Activated partial thromboplastin time
Bayley-III	Bayley Scale of Infant Development, third edition
BH4	Tetrahydrobiopterin
BL	Baseline
CBC	Complete blood count
cDNA	Complementary deoxyribonucleic acid
CMP	Comprehensive metabolic panel
CMV IEP	Cytomegalovirus immediate-early promoter
COVID-19	Coronavirus disease of 2019
CRO	Contract Research Organization
CSF	Cerebrospinal fluid
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
D	Day
DDC	DOPA decarboxylase (gene)
diff	Differential count
Disc	Discharge
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
eDiary	Electronic diary
ET	Early termination
GCP	Good Clinical Practice
hAADC	Human aromatic L-amino acid decarboxylase
HBG2/3	Human β globin partial intron 2/partial exon 3
HVA	Homovanillic acid
IB	Investigator's Brochure
ICF	Informed consent form
ICU	Intensive care unit
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
INR	International normalized ratio
IRB	Institutional Review Board
ITR	Inverted terminal repeat
L-DOPA	L-3,4-dihydroxyphenylalanine
MBq	Megabecquerel
mCi	Millicurie
MedDRA	Medical Dictionary for Regulatory Activities
MHPG	3-methoxy-4-hydroxyphenylglycol
MR	Magnetic resonance

Abbreviation or Specialized Term	Explanation
MRI	Magnetic resonance imaging
OGC	Oculogyric crisis/crises
PD	Pharmacodynamics
PDMS-2	Peabody Developmental Motor Scale, second edition
PET	Positron emission tomography
PI	Principal investigator
Poly A	Polyadenylation sequence
PT	Prothrombin time
PTT	Partial thromboplastin time
rAAV2	Recombinant adeno-associated virus, serotype 2
RBC	Red blood cell (count)
SAE	Serious adverse event
SOC	System Organ Class
SUV	Standardized uptake value
SUV_{max}	Maximal standardized uptake value
T1-MPRAGE	T1-weighted magnetization prepared rapid gradient echo
T2-FLAIR	T2-weighted fluid-attenuated inversion recovery
TEAE	Treatment-emergent adverse event
vg	Vector genomes
W	Week
WBC	White blood cell (count)

1. INTRODUCTION

This study will be conducted in full accordance with the International Council for Harmonisation (ICH), Good Clinical Practice (GCP) Consolidated Guideline (E6), and any applicable national and local laws and regulations (eg, Code of Federal Regulations Title 21, Parts 50, 54, 56, 312, and 314; European Union Directive 2001/20/EC on the approximation of the laws, regulations, and administrative provisions of the Member States relating to the implementation of GCP in the conduct of clinical studies of medicinal products for human use). Standard medical care (prophylactic, diagnostic, and therapeutic procedures) will be the responsibility of the treating physician of the subject during the course of the study.

1.1. Background Information

1.1.1. Aromatic L-amino Acid Decarboxylase Deficiency

Aromatic L-amino acid decarboxylase (AADC) deficiency is a monogenetic disorder of neurotransmitter synthesis that manifests in young children and most commonly results in complete arrest of motor development. AADC deficiency is a rare, autosomal recessive metabolic disorder resulting from mutations in the DOPA decarboxylase (*DDC*) gene that encodes for AADC. The *DDC* gene is located on chromosome 7p12.1-7p12.3 and contains 15 exons. The AADC enzyme, which has 480 amino acids, is highly conserved across species and is expressed in the brain, sympathetic ganglia, and adrenal medulla. A total of 82 *DDC* variants have been identified and cataloged. Of these, 79 variants are known to lead to AADC deficiency (Wassenberg 2017).

Patients with AADC deficiency have a wide range of clinical presentation. Patients may have some symptoms at birth, develop others a few weeks or months later, and symptoms in some cases may fluctuate in intensity and frequency (Brautigam 2000, Helman 2014). Of the limited reported cases of AADC deficiency, all patients had symptoms within the first year of life (mean age of 2.7 months) (Brun 2010, Wassenberg 2017). The mean age of diagnosis was about 3.5 years, indicating the difficulties in recognizing the disease and subsequent delays in diagnosis (Brun 2010, Wassenberg 2017).

The AADC enzyme deficiency results in a marked or complete loss of dopamine and serotonin production in the brain from birth. Consequently, AADC-deficient patients exhibit symptoms related to loss in dopamine signaling, affecting voluntary movements, cognitive functions, and emotion. Patients with AADC deficiency have arrested motor development despite essentially preserved neurophysiology and neuroanatomy as determined by brain imaging. These patients fail to achieve motor milestones typical of healthy children, such as full head control and ability to sit, stand, or walk. Patients also experience intellectual disability and show irritability, and are at risk of early death in the first decade of life (Korenke 1997, Pons 2004, Helman 2014).

Eladocagene exuparvovec (AGIL-AADC) is a recombinant adeno-associated virus, serotype 2 (rAAV2)-based gene therapy containing human AADC (h*AADC*) complementary deoxyribonucleic acid (cDNA). The rAAV2 vector delivers cDNA encoding a normal copy of the hAADC enzyme. This results in the production of functional AADC enzyme and completion of the biosynthesis of dopamine, enabling development of motor functions in patients with AADC deficiency. All patients with AADC deficiency can benefit from this gene therapy that targets the underlying cause of the disease (ie, mutation in the *DDC* gene that leads to AADC deficiency).

Currently, eladocagene exuparvovec (Upstaza) is approved in the European Union and the United Kingdom. No other drug or gene therapy is approved for the treatment of AADC deficiency. Drug therapies presently prescribed for AADC deficiency are primarily intended to treat symptoms, and do not treat the underlying cause of the disease. Available pharmacological interventions include dopamine agonists, monoamine oxidase inhibitors, and pyridoxine therapies (Himmelreich 2019). Most patients, particularly those with no motor development, do not respond to available treatments because these therapies cannot replace or increase dopamine production in the brain to adequately improve motor function and allow achievement of developmental milestones (Brun 2010). AADC deficiency typically results in death in the first decade of life (National Center for Advancing Translational Sciences 2018). The lack of effective treatment clearly indicates that AADC deficiency is a high unmet medical need, and that therapies to treat AADC deficiency are urgently needed to provide lasting and clinically meaningful improvement in motor development and function.

1.2. Stage of Development

The eladocagene exuparvovec clinical program to date consists of 3 completed clinical studies and 1 ongoing long-term follow-up study in subjects with AADC deficiency. All studies are single-arm trials in which subjects received treatment with eladocagene exuparvovec. The first 3 studies were conducted at the same center in Taiwan, the National Taiwan University Hospital. The efficacy findings across the studies were similar indicating the reproducibility of the following results:

- Study AADC-CU/1601 (N=8) is completed and was a Phase 1 observational study that summarized data from an interventional, compassionate use program of subjects with AADC deficiency followed for 60 months (5 years). Evidence of a favorable safety profile and durable clinical benefit observed in the follow-up period of Study AADC-CU/1601 justified continued clinical development of eladocagene exuparvovec for treatment of AADC deficiency.
- Study AADC-010 (N=10) is a completed, Phase 1/2, prospective, 60-month study; all subjects have been treated, with an average follow-up of 60 months (range 12 to 62 months).
- Study AADC-011 (N=12) is a completed Phase 2b, prospective, 13-month study. All subjects have been with an average follow-up of 12.5 months.

Additionally, Study AADC-1602 is an ongoing long-term follow-up of subjects who were treated with eladocagene exuparvovec in Studies AADC-CU/1601, AADC-010, and AADC-011. As of 16 June 2023, data for 26 subjects are available in this study and the mean duration of follow-up is 78.8 months (range 27.2 to 126.5 months).

The results of these clinical studies indicate that a single 1.8×10^{11} vector genomes (vg) or 2.4×10^{11} vg dose of eladocagene exuparvovec administered through bilateral putaminal infusion results in rapid, clinically meaningful, and durable improvements in motor function and achievement of motor milestones that would otherwise not be achieved, as evidenced by the natural history cohort (Wassenberg 2017). Significant improvement from baseline in both gross and fine motor skills, as assessed by Peabody Developmental Motor Scale, second edition (PDMS-2) and Alberta Infant Motor Scale (AIMS) scores, were observed across the studies. The

dosing regimen also resulted in improvement in cognitive function and a reduction in neurologic events, such as floppiness (hypotonia) and dystonia.

1.3. Trial Rationale

The primary aims of this study are to demonstrate a post-therapy increase in homovanillic acid (HVA) and to establish the safety of the SmartFlow magnetic resonance (MR)-compatible ventricular cannula in the administration of eladocagene exuparvovec to subjects with AADC deficiency.

HVA is a main metabolite of dopamine and HVA cerebrospinal fluid (CSF) levels are recognized as a proxy for dopamine levels in the brain. Given that dopamine depletion is the key element of the pathology of AADC deficiency, restoration of dopamine is the direct result of the gene therapy and is necessary for clinical benefit. The ability of HVA to reflect aberrant dopamine levels in the striatum in patients with AADC deficiency is supported by the fact that the treatment guidelines for AADC deficiency uses CSF HVA levels as one of the diagnostic criteria for the disease (Wassenberg 2017).

Results from the previous 3 eladocagene exuparvovec studies support the use of change from baseline in CSF HVA levels as likely to predict clinical benefit. The results show the following:

- Low levels of HVA at baseline are consistent with low dopamine levels on positron emission tomography (PET) imaging and with profound dopamine-related motor defects.
- Following treatment, there was a statistically significant increase in CSF HVA levels that corresponded to de novo dopamine production—a direct result of the gene therapy.
- A strong correlation existed between change from baseline in post-treatment CSF HVA levels and long-term clinical benefit.

The safety and efficacy of eladocagene exuparvovec delivered by direct injection into the bilateral putamen via established stereotactic procedures using commercially available guidance systems has already been established in 3 clinical studies (Studies AADC-CU/1601, AADC-010, and AADC-011). The results from all 3 clinical studies showed that subjects treated with eladocagene exuparvovec initiated motor development that would otherwise not have likely developed. The cannula used in these prior studies to deliver gene therapy was manufactured by Eicom in Japan and is not available for commercial use in the United States. Therefore, this open-label study is being conducted with the MR-compatible ventricular cannula, which is available for commercial use in the United States, to establish safety of its use in administration of eladocagene exuparvovec to the putamen of pediatric subjects.

The SmartFlow MR-compatible ventricular cannula has been used to administer eladocagene exuparvovec in the European Union both commercially and via early access programs and was also used previously to administer a similar viral vector to the putamen of adult subjects to treat Parkinson's disease (Bankiewicz 2016, Christine 2019). The device will allow precise targeting of the putamen using stereotactic positioning of the cannula through the use of intraoperative magnetic resonance imaging (MRI). Because AADC deficiency is a rare disorder and because the method of administering treatment requires a neurosurgical procedure, a control group in which subjects are administered placebo or undergo a sham procedure will not be used.

1.4. Risk-Benefit Assessment

AADC deficiency is a debilitating disease that results in near or complete arrest of motor development. AADC is an enzyme responsible for the decarboxylation of L-3,4-dihydroxyphenylalanine (L-DOPA) and 5-hydroxytryptophan (5-HTP) and is the final step in dopamine synthesis. Dopamine is required in the brains of humans to develop motor function. Without adequate levels of AADC, children exhibit stunted motor development and fail to develop motor milestones. Patients with AADC deficiency require lifelong care and their condition does not improve without intervention. Current treatments for AADC deficiency alleviate symptoms, but do not address the underlying cause of the disease.

Eladocagene exuparvovec is designed to increase levels of AADC within target areas of the brain, with the goal of restoring levels of dopamine. In children, dopamine signaling is required to develop motor skills in a sequential fashion. This study will evaluate the increase in HVA levels as an indication of dopamine increase following eladocagene exuparvovec treatment.

The safety and efficacy of eladocagene exuparvovec has been established in 3 clinical studies using a stainless-steel cannula. This study will evaluate the administration of eladocagene exuparvovec to pediatric subjects using the SmartFlow MR-compatible ventricular cannula, which will allow for intraoperative MRI (if required) to assist in guidance of gene therapy administration and has been used previously to administer viral vector to the brain of adult patients with Parkinson's disease (Bankiewicz 2016).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary Objectives

The primary objectives of this study are as follows:

- To assess the pharmacodynamics (PD) of eladocagene exuparvovec treatment by evaluation of HVA levels at 8 weeks after administration
- To assess the safety of the SmartFlow MR-compatible ventricular cannula for administering eladocagene exuparvovec to pediatric subjects.

2.2. Secondary Objectives

The secondary study objectives of the study are as follows:

- To assess the PD of eladocagene exuparvovec by evaluation of the following:
  - HVA at Week 48
  - PET at Weeks 8 and 48
  - 5-hydroxyindoleacetic acid [5-HIAA] at Weeks 8 and 48
  - 3-*O*-methyldopa [3-OMD]) at Weeks 8 and 48
- To evaluate the long-term efficacy of eladocagene exuparvovec through Month 60 as assessed by the following:
  - Motor milestone attainment
  - PDMS-2 score
  - Bayley Scale of Infant Development, third edition (Bayley-III)
  - EQ-5D-Y
  - Body weight
  - AADC-specific symptoms
- To evaluate the safety of eladocagene exuparvovec treatment as assessed by treatment-emergent adverse events (TEAEs), neurological examinations, MRI, and clinical laboratory tests.

2.3. Primary Endpoints

The primary efficacy endpoint is the change from baseline in HVA metabolite levels at the end of the Trial Phase (8 weeks after administration).

The primary safety endpoint is the assessment of adverse events (AEs) associated with the surgical administration of eladocagene exuparvovec to pediatric subjects using the SmartFlow MR-compatible ventricular cannula at the end of Trial Phase (8 weeks after administration).

2.4. Secondary Endpoints

The secondary endpoints are as follows:

- Change from baseline in neurotransmitter CSF metabolite HVA (at 48 weeks after administration)
- Change from baseline in PET imaging of putaminal-specific L-6-[^{18}F] fluoro-3,4-dihydroxyphenylalanine (^{18}F-DOPA) PET uptake at the end of the Trial Phase (8 weeks after administration) and the Extension Phase (48 weeks after administration)
- Change from baseline in neurotransmitter CSF metabolites 5-HIAA and 3-OMD at 8 and 48 weeks after administration
- Attainment of motor milestones
- Motor development as assessed by the PDMS-2
- Cognitive and language development as assessed by Bayley-III
- Change in EQ-5D-Y
- Change in body weight
- Assessment of AADC-specific symptoms
- Overall safety profile characterized by type, frequency, severity, timing, and relationship to study treatment of any TEAEs, neurological examination findings, brain imaging, or laboratory abnormalities.

3. STUDY DESCRIPTION

3.1. Study Design

This is an open-label study in subjects with AADC deficiency. At minimum, 3 eligible pediatric subjects will be enrolled and receive eladocagene exuparvovec at 1.8×10^{11} vg via SmartFlow MR-compatible ventricular cannula in a single operative session. Subjects will receive standard of care for their AADC deficiency during the study. Subjects will undergo Screening and a Baseline Visit before receiving eladocagene exuparvovec by intraputaminal infusion. A Data Safety Monitoring Board (DSMB) will conduct a review of safety data as outlined in the DSMB charter. Review by DSMB will not be required in order to enroll successive subjects. The DSMB will monitor ongoing study results to ensure subject well-being, safety, and study integrity. Subjects will return for regular visits during the course of the study. The length of the study, including the Screening Window, is approximately 63 months (approximately 5 years).

This study's Trial Phase, Extension Phase, and Long-Term Extension Phase are described as follows:

- The primary objectives of the Trial Phase are to assess:
  - the PD of eladocagene exuparvovec treatment by evaluation of HVA levels at 8 weeks after administration
  - the safety of the SmartFlow MR-compatible ventricular cannula for administering eladocagene exuparvovec to pediatric subjects with AADC deficiency.
- The secondary objectives of the Trial Phase are to further assess the PD of eladocagene exuparvovec in subjects with AADC deficiency to further assess the PD of eladocagene exuparvovec in subjects with AADC deficiency using neurotransmitter metabolite assessment and PET analysis.
- The Extension Phase is designed to capture additional clinical information for eladocagene exuparvovec through study evaluations, changes in motor development, AADC-specific- symptoms, and other PD measures. The Extension Phase will be complete at 48 weeks after administration of eladocagene exuparvovec. The additional study evaluations will be assessed as shown in the Schedule of Events in Table 1 and Table 2.
- The Long-Term Extension Phase is designed to capture long-term safety and efficacy data, from subjects treated with eladocagene exuparvovec, through Month 60. Study evaluations for this Phase will be assessed as shown in the Schedule of Events in Table 3.

3.2. Justification of Dose

Strong nonclinical data in nonhuman primate models of Parkinson's disease and clinical data in patients with Parkinson's disease with rAAV2-h*AADC* vectors delivered to the putamen were used to guide the dose selection for a one-time administration of eladocagene exuparvovec for treating AADC deficiency. The intended dose of 1.8×10^{11} vg balances positive efficacy assessments with safety, as evidenced by the results from the 3 clinical studies.

Intrastriatal (caudate/putamen) and intraputaminal (putamen only) delivery of rAAV2-h*AADC* vectors in a nonhuman primate model of Parkinson's disease resulted in AADC protein expression and improvements in response to L-DOPA therapy as evaluated by neurological function (Muramatsu 2002). Doses tested in the different studies were from 6×10^{9} to 3.6×10^{11} vg. Forsayeth and colleagues assessed multiple doses within a single preclinical Parkinson's disease study (Forsayeth 2006). They evaluated the relationship between rAAV2-h*AADC* dose infused into the putamen and efficacy, including AADC enzyme activity in hemiparkinsonian monkeys.

The doses tested ranged from 6×10^{9} to 5×10^{11} vg. The study found that vector dose produced a linear increase in AADC enzyme activity in brain tissue at doses $<5.5\times10^{10}$ vg followed by a plateau starting at dose 1.7×10^{11} vg, indicating a saturation phenomenon in which higher doses showed little additional AADC enzyme activity. These results suggest that doses above 1.7×10^{11} vg produce little additional increase in expression of rAAV2-h*AADC* transgene (Forsayeth 2006). In the context in which there are no demonstrable gains in efficacy at higher doses, it becomes imperative to ensure safety.

Based on the dose response efficacy observed in nonhuman primate Parkinson's disease studies, rAAV2-h*AADC* was subsequently tested in the first-in-human clinical trials of patients with Parkinson's disease at dose levels of 9×10^{10} and 3×10^{11} vg via bilateral intraputaminal dosing (Christine 2009, Muramatsu 2010). Both doses were biologically active and well tolerated (Christine 2009). The prior findings in Parkinson's disease patients were used to establish a dose that was expected to improve AADC activity in the putamen of children with AADC deficiency.

The intended dose of 1.8×10^{11} vg is based on the fact that AADC activity and clinical benefit and safety have been demonstrated in 3 separate clinical studies with a follow-up of up to 9 years post administration of eladocagene exuparvovec.

Eladocagene exuparvovec will be administered intraoperatively as a 1-time dose as four 0.08 mL infusions at a dose of 0.45×10^{11} vg and a volume of 80 µL per site to 4 sites (2 per putamen), for the total dose of 1.8×10^{11} vg and a total volume of 320 µL per patient.

3.3. End of Study Definition

The end of study (Trial Phase, Extension Phase, and Long-Term Extension Phase) is defined as completion of assessments at the Month 60 Visit, or after follow-up for those subjects who complete the early termination (ET) visit or who decide to withdraw study consent. For subjects that terminate the study before the Week 48 visit, the ET Visit will be completed and will include all assessments required at the Week 48 visit. For subjects that terminate the study after the Week 48 visit, but prior to the Month 60 Visit, the ET Visit will be completed and will include all assessments required at the Month 60 Visit.

4. STUDY POPULATION

4.1. Inclusion Criteria

Subjects will be included if all the following inclusion criteria are fulfilled:

1. Pediatric subjects must have genetically confirmed AADC deficiency with typical clinical characteristics and decreased AADC enzyme activity in plasma.
2. Age range from 1 year to <18 years.
3. Cranium sufficiently developed to allow placement of ClearPoint system for stereotactic surgery.
4. Persistent neurological defects secondary to AADC deficiency despite standard medical therapy (dopamine agonists, monoamine oxidase inhibitor, pyridoxine, or other forms of vitamin B6) in the opinion of the investigator.
5. Unable to ambulate independently (with or without assistive device).
6. Baseline hematology, chemistry, and coagulation values within the normal pediatric laboratory value ranges, unless in the investigator's opinion the out-of-range values are not clinically significant with respect to the subject's suitability for surgery.
7. Subject must test negative for coronavirus disease of 2019 (COVID-19) a maximum of 72 hours prior to receiving gene therapy.

   Note: If a subject tests positive for COVID-19 at the Screening or Baseline Visit, he/she will need to have negative test results for 2 weeks (2 weeks since the last positive test result and 2 negative test results a minimum of 14 days apart, with second negative test result no more than 72 hours prior to surgery) before receiving gene therapy. If a COVID-19 test is administered per site policy within 72 hours of the Screening Visit, the results may be used for the AADC-GT-002 study. The COVID-19 test does not need to be repeated after the COVID-19 pre-consent is signed.
8. Subject must be on stable dosage for 3 months prior to baseline for all medications related to treatment of AADC deficiency, including dopamine agonists, monoamine oxidase inhibitors, anticholinergic drugs, and vitamin B6.
9. Females of childbearing potential must have a negative pregnancy test at screening and baseline and agree to abstinence or double-barrier form of contraception for the duration of the study following discharge from the hospital (acceptable methods will be determined by the site).
10. Males sexually active with females of childbearing potential must agree to use a barrier method of birth control during the study following discharge from the hospital.
11. Parent(s)/legal guardian(s) with custody of the subject must agree to comply with the requirements of the study, including the need for frequent and prolonged follow-up.
12. Parent(s)/legal guardian(s) with custody of the subject must give their consent for subject to enroll in the study.

4.2. Exclusion Criteria

1. The subject has presence of other significant medical or neurological conditions that would create an unacceptable operative or anesthetic risk.
2. Subjects with pyridoxine 5'-phosphate oxidase or tetrahydrobiopterin (BH4) deficiency.
3. Contraindication for imaging studies (computed tomography [CT] scan, PET, or MRI), including sedation limitations or metal that would interfere with a brain MRI.
4. Anti-AAV2 antibody titer higher than 1:1200 or >1 optical density value by enzyme-linked immunosorbent assay.
5. Subjects that have received treatment with other experimental therapies within the last 24 weeks prior to planned gene therapy administration, or any treatment ever with a gene therapy.
6. Evidence of a clinically active infection.
7. Females who are pregnant or breast feeding.

4.3. Screen Failures

Only subjects who fail screening assessments/procedures due to a positive COVID-19 test will be permitted to rescreen.

If a subject withdraws consent prior to dosing, he or she may rescreen at a later date after the investigator's discussion with the PTC medical monitor.

5. STUDY INTERVENTION

The eladocagene exuparvovec nonclinical program consists of proprietary studies, including in vitro studies in human cells, as well as relevant supportive literature information that explored efficacy studies in a mouse model of AADC deficiency and rat and nonhuman primate models of Parkinson's disease. Details of these studies and the selection of the intraputaminal route of administration are provided in Section 4 of the Investigator's Brochure (IB).

See the Surgical Manual for a complete description of the surgical procedure.

5.1. Study Intervention Description

Eladocagene exuparvovec is a recombinant non-replicating AAV2 vector comprising a human *DDC* (also referred to as *AADC*) cDNA transcript, which encodes hAADC, under the control of the cytomegalovirus immediate-early promoter (CMV IEP) and simian virus 40 polyadenylation transcription terminator (Figure 1).

Figure 1: Diagram of Eladocagene Exuparvovec Expression Cassette

Abbreviations: CMV IEP, cytomegalovirus immediate-early promoter; hAADC, human aromatic L-amino acid decarboxylase; HBG2/3, human β globin partial intron 2/partial exon 3; ITR, inverted terminal repeat; Poly A, polyadenylation sequence
Note: Genetic elements are drawn to approximate proportions.
Source: Eladocagene exuparvovec IB, Figure 1

Eladocagene exuparvovec is formulated in a sterile solution containing standard compendial excipients.

5.2. Dosing and Administration

Subjects will receive eladocagene exuparvovec intraoperatively as a 1-time dose as four 0.08 mL infusions at a dose of 0.45×10^{11} vg and a volume of 80 µL per site to 4 sites (2 per putamen), for the total dose of 1.8×10^{11} vg and a total volume of 320 µL per subject. Administration of gene therapy is described in the Surgical Manual.

5.3. Preparation/Handling/Storage/Accountability

5.3.1. Preparation and Handling

Details pertaining to the preparation and handling of eladocagene exuparvovec are provided in the Pharmacy Manual.

5.3.2. Storage

Eladocagene exuparvovec will be stored at ≤-65°C. Study personnel must ensure that all eladocagene exuparvovec drug product is kept in a temperature monitored secure locked area with access limited to authorized personnel. Temperature excursions must be reported immediately, and product must be quarantined while awaiting disposition confirmation from the sponsor.

5.3.3. Accountability

Gene therapy will be administered on a one-time basis by a neurosurgeon.

The investigator/site personnel and/or central pharmacy must maintain accurate records of the receipt of all gene therapy shipped by PTC Therapeutics (PTC), or its designee, including, but not limited to, the date received, lot number, amount received, and the disposition of all gene therapy product. Drug accountability records must also be maintained by the site and central pharmacy that include the subject's assigned study number, date and amount of gene therapy dispensed, and relevant kit and lot numbers.

5.3.4. Formulation, Appearance, Packaging, and Labeling

Eladocagene exuparvovec is an AAV2 capsid containing the expression cassette with the h*AADC* gene of interest (see Section 5.1). The final commercial formulation of eladocagene exuparvovec will be used in this study. The drug product is comprised of compendial excipients including potassium chloride, sodium chloride, potassium dihydrogen phosphate, disodium hydrogen phosphate, and poloxamer 188 in Water for Injection, pH 6.9.

Additional details can be found in the IB and the Pharmacy Manual.

5.4. Concomitant Therapy

Other than the gene therapy, any treatments (including prescription and non-prescription drugs, health foods, herbal remedies, or self-prescribed drugs) that are taken by a subject during the Screening Window, during gene therapy administration, and for the remainder of the study are considered concomitant medications. Information regarding any concomitant medications will be collected and documented in the electronic case report form (eCRF) and in the source documents by the clinic staff.

To the extent possible, administration of any prescription or over-the-counter drug products other than study medication should be minimized during the study period. Subjects should be discouraged from use of "health supplements" (eg, creatine, glutamine), herbal remedies, growth hormone, or self-prescribed drugs at any time during this clinical study of eladocagene exuparvovec. Blood thinners should not be used 7 days prior to the surgical procedure.

Any medication that may affect the result evaluation of trials cannot be used during the trial stage.

All medications related to the treatment of AADC deficiency, including dopamine agonists, monoamine oxidase inhibitors, anti-cholinergic drugs, and vitamin B6, may be continued during the study provided that:

- no changes in dosage for the 3 months prior to baseline

- change in the dosage during the duration of the trial is not anticipated, with the exception of an allowance for decrease in dosage or discontinuation in the setting of a hyperdopaminergic state. Dosing changes are made at the discretion of the investigator

If considered necessary for the subject's well-being, drugs for concomitant medical conditions or for symptom management may be given at the discretion of the investigator. The decision to authorize the use of any other drug(s) should consider the subject's safety, the medical need, the potential for drug interactions, the possibility for masking symptoms of a more relevant underlying event, and whether use of a concomitant medication will compromise the outcome or integrity of the study.

Subjects and parents/caregivers or legal guardian should be instructed about the importance of the need to inform the clinic staff of the use of any drugs or remedies (whether prescribed, over-the-counter, or illicit) before and during the course of the study.

Vaccination for COVID-19 is permissible as a concomitant medication under the following conditions:

- The subject must wait 1 month after the final dose of vaccine prior to receiving eladocagene exuparvovec.
- Once the subject has been dosed with eladocagene exuparvovec, it is recommended that he/she waits 3 months from the date of eladocagene exuparvovec administration before receiving the vaccine.

Vaccine information should be recorded with the subject's concomitant medications.

The investigator is encouraged to consult the PTC medical monitor or designee with questions relating to specific drugs and their potential for interactions with eladocagene exuparvovec.

5.5. Organ Donation

Subjects may not donate blood, organs, tissues, or fluids at any time during the study or after the study has been completed.

6. STUDY INTERVENTION DISCONTINUATION AND SUBJECT DISCONTINUATION/WITHDRAWAL

6.1. Stopping Rules

The procedure will be discontinued in the event of any occurrence that would potentially lead to intraoperative or postoperative complications or increased risk of subject harm.

At the subject level, the occurrence of any of the following events, regardless of causality, would lead to discontinuation of the procedure for any subject:

- Anesthesia complications
- Intracerebral hemorrhage demonstrated on imaging during the procedure
- Hemodynamic instability during the procedure
- Equipment malfunction
- Presence of a clinically significant CSF leak, in the opinion of the investigator, during the study procedure

At the study level, the occurrence of any of the following events, regardless of causality, would lead to halting of study enrollment:

- Any symptomatic intracerebral hemorrhage or stroke that results in a significant new neurologic deficit that persists one month following surgery
- Clinically significant CSF leak, in the opinion of the investigator
- Any central nervous system infections related to study interventions
- Dyskinesias severe enough to require intensive care unit (ICU) admission for greater than 30 days
- Any death

If any of these events occur, no further subjects will receive treatment until a comprehensive safety review has been completed by the DSMB and PTC. The United States Food and Drug Administration (FDA) and/or applicable country health authority(ies), Institutional Review Boards (IRBs), Institutional Ethics Committees, and the Institutional Biosafety Committee will be promptly notified.

6.2. Participant Discontinuation/Withdrawal from the Study

This study features a one-time administration of gene therapy via surgical procedure. Subjects may discontinue from the study at any time.

If it is determined by the investigator that any subject will discontinue the study, all ET Visit procedures should be completed according to Table 2 for the Extension Phase and Table 3 for the Long-Term Extension Phase, and the Final Visit should be captured as ET in an eCRF. If it is determined that a subject will discontinue the study in between visits, the subject should return at their earliest convenience for an ET Visit to complete any required study assessments. The PTC medical monitor should be informed within 24 hours of the investigator being made aware of the subject's discontinuation of the study via e-mail.

Subjects who terminate the study early will not be replaced.

- All subjects who receive eladocagene exuparvovec should remain in the study for the duration of the study. However, the subject, parent/caregiver, or legal guardian has the right to withdraw consent and discontinue the study at any time.

A subject may withdraw/discontinue under the following conditions/events:

- The occurrence of a clinically significant worsening of disease status or change in a laboratory parameter that may place the subject at risk.
- The occurrence of a SAE.
- The occurrence of a protocol violation, if it interferes with the safety of a subject or data integrity.
- Upon consultation with the PTC medical monitor, the investigator may withdraw the subject from the study if, in the investigator's clinical judgment, it is not in the subject's best interest to continue.
- This study may be discontinued by the relevant regulatory authority, IRB/Independent Ethics Committee (IEC), and/or PTC at any time.

6.3. Lost to Follow-Up

Subjects are considered lost to follow-up if the subject does not return to the clinic and attempts to contact the subject or subject's parent/caregiver/legal guardian are unsuccessful. The site should make every effort to avoid any subject being lost to follow-up during the study. Before subjects are considered lost to follow-up, a minimum of 2 documented telephone contact attempts and 1 certified letter within 6 weeks of the most recent planned study visit must be sent in efforts to contact the subject/caregiver/legal guardian. After being considered lost to follow-up, a subject's status may be changed if the subject/caregiver/legal guardian makes contact at a later time provided the trial is ongoing.

7. STUDY ASSESSMENTS AND PROCEDURES

7.1. Schedule of Events and Study Parameters

Table 1: Schedule of Events for Trial Phase

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Type of Visit (In-Person or Phone)	**In-Person**	**In-Person**	**In-Person**	**In-Person**	**Phone**	**In-Person**	**Phone**	**Phone**	**In-Person**
Visit Window[a]	**W-10 to -2**	**BL W-1**	**Dosing Day (D1)[c]**	**Disc (D3)**	**W2**	**W3**	**W4**	**W6**	**W8**
	Screening[b]	**±3D**		**+4D**	**±2D**	**±3D**	**±2D**	**±2D**	**±3D**
Informed consent	X								
Inclusion/exclusion criteria	X	X							
Genetic testing[d,e,f]	X								
Demography	X								
Medical history	X								
COVID-19 test[g]	X	X	X						
Pregnancy test[h]	X	X	X			X			X
AADC enzyme activity assessment[f]	X								
Collect CSF history[i]	X								
CSF neurotransmitter analysis[f,j,k]			X[j,m,o]						X[j,o]
Anti-AAV2 antibody (IgG and neutralizing titers)[f]	X		X[l]	X		X			X
Viral shedding (blood and urine)[f,n]			X[l]	X		X			X
Viral shedding (CSF)[f,j]			X[j,m,o]						X[j,o]
Physical examination[p]	X	X	X	X		X			X
Vital signs[q]	X	X	X	X		X			X
Height/weight	X	X	X	X		X			X
Brain MRI (T1-MPRAGE and T2-FLAIR sequences)[j,o]	X[r]			X[s]		X[s]			X[s]
Real-time intrasurgical MRI			X						
Postdose brain CT[t]			X						
Brain ^{18}F-DOPA PET[j,o,u]		X							X
Chest x-ray[v]		X							
12 lead ECG		X							

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Type of Visit (In-Person or Phone)	**In-Person**	**In-Person**	**In-Person**	**In-Person**	**Phone**	**In-Person**	**Phone**	**Phone**	**In-Person**
Visit Window[a]	**W-10 to -2**	**BL W-1**	**Dosing Day (D1)[c]**	**Disc (D3)**	**W2**	**W3**	**W4**	**W6**	**W8**
	Screening[b]	**±3D**		**+4D**	**±2D**	**±3D**	**±2D**	**±2D**	**±3D**
Oculogyric crisis eDiary instructions for use[w]	X								
AADC-specific symptoms[x]	X	X		X		X			X
Laboratory tests[y]	X	X		X		X			X
T-cell sample collection	X		X	X		X			X
PDMS-2		X							
Bayley-III		X							
EQ-5D-Y[z]		X							
Study drug injection (eladocagene exuparvovec)			X						
AEs		X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X

Abbreviations: 3-OMD, 3-*O*-methyldopa; 5-HIAA, 5-hydroxyindoleacetic acid; ^{18}F-DOPA, fluoro-3,4-dihydroxyphenylalanine; AADC, aromatic L-amino acid decarboxylase (deficiency); AAV2, adeno-associated virus, serotype 2; AE, adverse event; aPTT, activated partial thromboplastin time; BL, Baseline; Bayley-III, Bayley Scale of Infant Development, third edition; CBC, complete blood count; CMP, comprehensive metabolic panel; COVID-19, coronavirus disease of 2019; CSF, cerebrospinal fluid; CT, computed tomography; D, day; diff, differential count; Disc, discharge; ECG, electrocardiogram; eDiary, electronic diary; HVA, homovanillic acid; ICU, intensive care unit; IgG, immunoglobulin G; INR, international normalized ratio; L-DOPA, L-3,4-dihydroxyphenylalanine; MHPG, 3-methoxy-4-hydroxyphenylglycol; MRI, magnetic resonance imaging; OGC, oculogyric crisis; PDMS-2, Peabody Developmental Motor Scale, second edition; PET, positron emission tomography; PI, principal investigator; PT, prothrombin time; PTT; partial thromboplastin time; RBC, red blood cell (count); T1-MPRAGE, T-1 weighted magnetization prepared rapid gradient echo; T2-FLAIR, T2-weighted fluid-attenuated inversion recovery; W, week; WBC, white blood cell (count)

[a] Any study visit may take place over a 3-day period, as necessary.

[b] Screening will be conducted and completed up to 9 weeks prior to the Baseline Visit. Subjects who are unable to adhere to the Screening Visit window specified in the protocol due to unforeseen circumstances (eg, COVID-19) may be rescreened upon sponsor approval. If the Baseline Visit does not occur within 9 weeks after the Screening Visit per the Screening Window, the only Screening Visit assessments that need to be performed again are the local laboratory assessments, physical exam, and vital signs.

[c] Surgical procedure will require a minimum of 1 night in the ICU and hospitalization for up to 3 days. Subjects will be required to stay in the vicinity of the study clinic for a minimum of 7 days total post procedure.

[d] If historic AADC diagnosis clinical testing results are available, they may be used to determine eligibility. If historic AADC diagnosis clinical testing results are used to determine eligibility, AADC diagnosis clinical testing does not need to be repeated at Screening.

[e] If historic enzyme results are available, they may be used to determine eligibility. If historic enzyme results are used to determine eligibility, enzyme testing does not need to be repeated at Screening.

[f] Analyzed by a Central Laboratory.

[g] Subjects must pre-consent and have a negative COVID-19 test prior to the Screening Visit. Subject must test negative for COVID-19 a maximum of 72 hours prior to receiving gene therapy. If a subject tests positive for COVID-19 at the Screening or Baseline Visit, he/she will need to have negative test results for 2 weeks (2 weeks since the last positive test result and 2 negative test results a minimum of 14 days apart, with the second negative test result no more than 72

hours prior to surgery) before receiving gene therapy. If a COVID-19 test is administered per site policy within 72 hours of the Screening Visit, the results may be used for the AADC-GT-002 study. The COVID-19 test does not need to be repeated after the COVID-19 pre-consent is signed.
[h] Females of childbearing potential only. The pregnancy test can be collected via urine or serum, at the discretion of the PI. Will be assessed by a local laboratory.
[i] CSF analysis history (check only HVA/5-HIAA/3-OMD/pterins/MHPG/L-DOPA/5-HTP) to be collected if available.
[j] Subjects may be admitted to the hospital and sedation may be used at the discretion of the PI.
[k] CSF analysis items (HVA/5-HIAA/3-OMD and cell count [appearance, RBC, WBC, protein, and glucose]).
[l] Sample should be collected predose on day of surgery.
[m] CSF sample will be collected predose during the surgical procedure for the purposes of assessing viral shedding and neurotransmitter analysis.
[n] Urine should be collected using a clean catch or catheter and stored in a sterile container.
[o] Days that require imaging or lumbar puncture can be split into 3-day visits, if necessary, provided that all clinical assessments (Bayley-III, EQ-5D-Y, and PDMS-2) are completed prior to any other assessments on Days 1, 2, or 3 of the visits.
[p] Complete physical examination at Screening, Baseline Visit, and on Dosing Day (D1), and targeted physical examination for all other visits. The complete physical examination will consist of an examination of the following: neurological assessment and assessments of general appearance, any changes to feeding tube placement or removal, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart, abdomen, and extremities. The targeted physical examination will consist of a neurological assessment, general appearance assessment, any changes to feeding tube placement or removal, and heart auscultation.
[q] Vital signs include temperature, pulse, respiratory rate, and blood pressure.
[r] Brain MRI with gadolinium performed at Screening to exclude subjects who may have pre-existing conditions.
[s] Brain MRI with gadolinium to check for persistent CSF leakage/fistula and inflammatory changes (eg, aseptic ventriculitis/meningitis). An MRI should be performed immediately if a CSF leak is suspected.
[t] Brain CT for postdose hemorrhage check should be performed within 6 hours after the end of surgery.
[u] PET scans will be centrally read.
[v] P-A and lateral chest x-ray.
[w] Parent/caregiver must complete eDiary or paper diary for each OGC occurrence throughout the Trial Phase and Extension Phase. In the event that the eDiary cannot be used, a paper version will be provided.
[x] Findings for AADC-specific symptoms will be collected at every in-person visit after D1. These assess for floppiness (hypotonia), limb and stimulus-provoked dystonia, and muscle power.
[y] Laboratory tests (PT; PTT or aPTT; INR; CBC w/diff; and CMP analysis [including total bilirubin]). These will be assessed by a local laboratory.
[z] The EQ-5D-Y will not be administered to subjects under 4 years of age. If the subject turns 4 during the study, the caregiver will complete the EQ-5D-Y per protocol after the subject turns 4.

Table 2: Schedule of Events for Extension Phase

Visit	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Type of Visit (In-Person or Phone)	**Phone**	**In-Person**	**Phone**	**Phone**	**In-Person**	**Phone**	**Phone**	**In-Person**	**Phone**	**Phone**	**In-Person**
Visit Window[a]	**W10**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48/ET[b]**
	±2D	**±3D**	**±2D**	**±2D**	**±3D**	**±2D**	**±2D**	**±3D**	**±2D**	**±2D**	**±3D**
Pregnancy Test[c]		X			X			X			X
CSF neurotransmitter analysis [d,e,f]											X
Anti-AAV2 antibody (IgG and neutralizing titers)[d]		X			X			X			X
Viral shedding (blood and urine)[d,g]		X			X			X			X
Viral shedding (CSF)[d,e,f]											X
Physical examination[h]		X			X			X			X
Vital signs[i]		X			X			X			X
Height/weight		X			X			X			X
Brain MRI (T1-MPRAGE and T2-FLAIR sequences)[e,j,k]											X
Brain ^{18}F-DOPA PET[e,j,l]											X
AADC-specific symptoms[m]		X			X			X			X
Laboratory tests[n]		X			X			X			X
T-cell sample collection		X			X			X			X
PDMS-2					X[o]						X[o]
Bayley-III					X						X
EQ-5D-Y[p]					X						X
AEs	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X

Abbreviations 3-OMD, 3-*O*-methyldopa; 5-HIAA, 5-hydroxyindoleacetic acid; ^{18}F-DOPA, fluoro-3,4-dihydroxyphenylalanine; AADC, aromatic L-amino acid decarboxylase (deficiency); AAV2, adeno-associated virus, serotype 2; AE, adverse event; aPTT, activated partial thromboplastin time; Bayley-III, Bayley Scale of Infant Development, third edition; CBC, complete blood count; CMP, comprehensive metabolic panel; CSF, cerebrospinal fluid; D, day; diff, differential count; ET, early termination; HVA, homovanillic acid; INR, international normalized ratio; IgG, immunoglobulin G; MRI, magnetic resonance imaging; PDMS-2, Peabody Developmental Motor Scale, second edition; PET, positron emission tomography; PI, principal investigator; PT, prothrombin time; PTT; partial thromboplastin time; RBC, red blood cell (count); T1-MPRAGE, T-1 weighted magnetization prepared rapid gradient echo; T2-FLAIR, T2-weighted fluid-attenuated inversion recovery; W, week; WBC, white blood cell (count)

[a] Any study visit may take place over a 3-day period, as necessary.

[b] For subjects that terminate the study before the Week 48 visit, all assessments noted in the Week 48 visit will need to be completed.

[c] Females of childbearing potential only. The pregnancy test can be collected via urine or serum, at the discretion of the PI. Will be assessed by a local laboratory.

[d] Analyzed by a Central Laboratory.

[e] Subjects may be admitted to the hospital and sedation may be used at the discretion of the PI.

[f] CSF analysis items (HVA/5-HIAA/3-OMD and cell count [appearance, RBC, WBC, protein, and glucose]).

[g] Urine should be collected using a clean catch or catheter and stored in a sterile container.
[h] Complete physical examination at Screening, Baseline Visit, and on Dosing Day (D1) and targeted physical examination for all other visits. The complete physical examination will consist of an examination of the following: neurological assessment and assessments of general appearance, any changes to feeding tube placement or removal, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart, abdomen, and extremities. The targeted physical examination will consist of a neurological assessment, general appearance assessment, any changes to feeding tube placement or removal, and heart auscultation.
[i] Vital signs include temperature, pulse, respiratory rate, and blood pressure.
[j] Days that require imaging or lumbar puncture can be split into 3-day visits if necessary, provided that all clinical assessments (Bayley-III, EQ-5D-Y, and PDMS-2) are completed prior to any other assessments on Days 1, 2, or 3 of the visits.
[k] Brain MRI with gadolinium to check for persistent CSF leakage/fistula and inflammatory changes (eg, aseptic ventriculitis/meningitis). An MRI should be performed immediately if a CSF leak is suspected.
[l] PET scans will be centrally read.
[m] Findings for AADC-specific symptoms will be collected at every in-person visit. These assess for floppiness (hypotonia), limb and stimulus-provoked dystonia, and muscle power.
[n] Laboratory tests (PT; PTT or aPTT; INR; CBC w/diff; and CMP analysis [including total bilirubin]). These will be assessed by a local laboratory.
[o] Administer at approximately the same time of day as the baseline test was administered.
[p] The EQ-5D-Y will not be administered to subjects under 4 years of age. If the patient turns 4 during the study, the caregiver will complete the EQ-5D-Y per protocol after the patient turns 4.

Table 3: Schedule of Events for Long-Term Extension Phase

Visit	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**
Type of Visit (In-Person or Phone)	**Phone**	**In-Person**	**Phone**	**In-Person**	**Phone**	**In-Person**	**Phone**	**In-Person**	**Phone**	**In-Person**
Visit Window[a]	**W60**	**W72**	**W84**	**W96**	**W130 Month 30**	**W156 Month 36**	**W182 Month 42**	**W208 Month 48**	**W234 Month 54**	**W260 Month 60 ET[b]/EOS**
	±2D	**±3D**	**±2D**	**±2 weeks**	**±2 weeks**	**±6 weeks**	**±2 weeks**	**±6 weeks**	**±2 weeks**	**±6 weeks**
Pregnancy Test[c]		X		X		X		X		X
Physical examination[d]		X		X		X		X		X
Vital signs[e]		X		X		X		X		X
Height/weight		X		X		X		X		X
AADC-specific symptoms[f]		X		X		X		X		X
Laboratory tests[g]				X		X		X		X
PDMS-2		X[h]		X[h]		X[h]		X[h]		X[h]
Bayley-III		X		X		X		X		X
EQ-5D-Y[i]		X		X		X		X		X
AEs	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X

Abbreviations: 3AADC, aromatic L-amino acid decarboxylase (deficiency); AE, adverse event; aPTT, activated partial thromboplastin time; Bayley-III, Bayley Scale of Infant Development, third edition; CBC, complete blood count; CMP, comprehensive metabolic panel; D, day; diff, differential count; ET, early termination; PDMS-2, Peabody Developmental Motor Scale, second edition; PI, principal investigator; PT, prothrombin time; PTT; partial thromboplastin time; RBC, red blood cell (count); W, week; WBC, white blood cell (count)

[a] All visits may take place over a 7-day period, as necessary.

[b] For subjects who terminate the study before the Month 60 visit, but after the W48 visit, all assessments noted in the Month 60 visit will need to be completed.

[c] Females of childbearing potential only. The pregnancy test can be collected via urine or serum, at the discretion of the PI. Will be assessed by a local laboratory.

[d] Complete physical examination at Weeks 96, 156, 208, and 260/ET and targeted physical examination at Week 72. The complete physical examination will consist of an examination of the following: neurological assessment and assessments of general appearance, any changes to feeding tube placement or removal, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart, abdomen, and extremities. The targeted physical examination will consist of a neurological assessment, general appearance assessment, any changes to feeding tube placement or removal, and heart auscultation.

[e] Vital signs include temperature, pulse, respiratory rate, and blood pressure.

[f] Findings for AADC-specific symptoms will be collected at every in-person visit. These assess for floppiness (hypotonia), limb and stimulus-provoked dystonia, and muscle power.

[g] Laboratory tests (PT; PTT or aPTT; INR; CBC w/diff; and CMP analysis [including total bilirubin]). These will be assessed by a local laboratory.

[h] Administer at approximately the same time of day as the baseline test was administered.

[i] The EQ-5D-Y will not be administered to subjects under 4 years of age. If the patient turns 4 during the study, the caregiver will complete the EQ-5D-Y per protocol after the patient turns 4.

7.2. Primary Endpoints

7.2.1. HVA Levels

The precursor L-DOPA is decarboxylated by AADC to form dopamine. After action at the nerve synapse, dopamine is reabsorbed into the presynaptic nerve terminal where it can either be repackaged into vesicles for future neurotransmitter release or metabolized to HVA. In the presence of AADC deficiency, the HVA level in the CSF is very low or below the limit of detection due to the abnormally low dopamine production. Upon restoration of AADC activity, as premised with gene therapy, dopamine levels increase due to a now functioning *DDC* gene and the concentration of HVA in the CSF rises. Thus, HVA can serve as an acceptable measurement of dopamine production as a result of AADC activity (Hyland 2006, Hyland 2007).

7.2.2. Safety of Surgical Administration Using the SmartFlow Cannula

Adverse events associated with the surgical administration of eladocagene exuparvovec to pediatric subjects using the SmartFlow MR-compatible ventricular cannula that occur during the Trial Phase will be collected as described in Table 1.

7.3. Secondary Endpoints

7.3.1. ^{18}F-DOPA Positron Emission Tomography

Expression and activity of the AADC enzyme in the putamen will be assessed by PET imaging using ^{18}F-DOPA, a positron-emitting fluorine-labeled version of levodopa, which is a substrate for AADC that is incorporated into de novo dopamine. When ^{18}F-DOPA is administered intravenously, it crosses the blood-brain barrier and is taken up by presynaptic nigrostriatal dopaminergic neurons in the putamen and converted by AADC to dopamine (Firnau 1987). Therefore, increased ^{18}F-DOPA putamen uptake over time objectively demonstrates in vivo newly produced dopamine, and thus the presence of functional AADC enzyme.

^{18}F-DOPA will be infused during the procedure. In this study, a total dose of ^{18}F-DOPA will be administered consistent with the recommendations of the European Association of Nuclear Medicine task force and the prescribing information for DOPAVIEW. A weight-based dosage table is included in the Procedure Manual for PET Imaging of the Brain. A weight-based dose should be administered based on guidance in this table. Ninety minutes after injection of ^{18}F-DOPA, a 15-minute static acquisition will be obtained with a PET/CT scanner. The PET scanner detects positron emission radioactivity from ^{18}F-DOPA uptake, and the CT image provides brain anatomy; these images will be co-registered on the PET/CT scanner. PET imagining will be analyzed.

The levels of ^{18}F-DOPA radioactivity will be normalized by the injected dose and by subject weight and expressed as the standardized uptake value (SUV) using the open-source, free medical image viewer Horos (www.horosproject.org). Given that Swoboda and colleagues have previously reported that no ^{18}F-DOPA PET uptake could be measured in a single patient with AADC deficiency, it was decided to measure the maximal SUV in all regions of interest as previously reported by Hwu et al rather than average SUV (Swoboda 2003, Hwu 2012). Regions of interest for the putamen will be a 1-cm^2 circular area in the right and left putamen each, viewed on an axial plane. All values used will be the maximal SUV (SUV_{max}) for each brain

region described. The left and right putamen SUV_{max} will be subsequently averaged for a single putamen SUV_{max} measurement. The background brain radioactivity from any ^{18}F-DOPA that may still be present in the vasculature within the brain tissues will be subtracted from the putamen measurement using the occipital measurement (control region). The background SUV_{max} in the control region occipital lobe will be calculated from a 5-cm^2 area region of interest in the center of the occipital lobe.

7.3.2. Peabody Developmental Motor Scale, Second Edition

The PDMS-2 is a validated instrument used to measure motor skills and developmental milestone achievement in infants and children (Folio 2000).

To optimize testing duration in this pediatric population, for all subtests except for Reflexes, the PDMS-2 administrator may begin testing at an entry point, which is a predetermined item that most of children in the healthy population are able to achieve at a given age. A basal level will then be determined, which is the point at which the subject achieves a score of 2 on 3 consecutive skill items prior to achieving a 0 or 1 score on a skill item; all items below the basal level are scored as 2. Finally, a ceiling level is determined, which is the point at which the subject achieves a score of 0 on 3 consecutive skill items. All items above the ceiling are scored as 0, and the testing will be discontinued.

The PDMS-2 instrument is scored by a qualified physiotherapist. Each skill item is assessed as a simple, 3-level scoring system as a consistent way of describing the child's achievement of a particular motor skill, as listed below:

0 = the skill is not met

1 = the skill is emerging and shows a clear resemblance to mastery of the skill item

2 = the child is mastering the motor skill

A composite Gross Motor Quotient will be calculated from the scores on the Reflexes (8 skill items; age birth to 11 months), Stationary (30 skill items), Locomotion (89 skill items), and Object Manipulation (24 skill items; age 12 months and older) subscales. A composite Fine Motor Quotient will be calculated from the scores on the Grasping (26 skill items) and Visual Motor Integration (72 skill items) subscales. A Total Motor Quotient, which incorporates the results of both the Gross and Fine Motor Quotients, is considered the most complete evaluation of overall motor skills.

The PDMS-2 motor skill items assess key motor milestones of 1) full head control, 2) sitting unassisted, 3) standing with support, and 4) walking assisted, which were chosen for further statistical assessments as these were the key motor milestones used to define the natural history of patients with AADC deficiency (Wassenberg 2017). There are several components of each motor skill that become progressively more difficult. The PDMS-2 motor skill items that were used to assess motor milestones are described below:

- Full Head Control: A subject will be considered successful for Item 10 full head control if he/she achieves a score of 2 by sitting supported at his/her hips and holding his/her head aligned while rotating his/her head to follow a toy for 8 seconds, or if he/she achieves a score of 1 by sitting supported at his/her hips and holding his/her head aligned while rotating his/her head to follow a toy for 4 to 7 seconds.

- Sitting Unassisted: A subject will be considered successful in sitting unassisted if he/she achieves a score of 2 on Item 14 of the Stationary subtest, which requires the subject to sit without support and maintain balance while in a sitting position for 60 seconds, or if he/she achieves a score of 1, which requires the subject to sit without support and maintain balance while in a sitting position for 30 to 59 seconds.
- Standing with Support: A subject will be considered successful at stepping while standing with support if he/she achieves a score of 2 on Item 28 of the Locomotion (gross motor) subtest, which requires the subject to take at least 4 alternating steps, either in place or in forward motion, with the evaluator's hands around the child's trunk, consistent with standing with support, or if he/she achieves a score of 1, which requires the subject to take 2 to 3 alternating steps, either in place or in a forward motion, with the evaluator's hands around the child's trunk.
- Walking Assisted: A subject will be considered successful at walking with assistance if he/she achieves a score of 2 on Item 34 of the Locomotion (gross motor) subtest, which requires the subject to walk at least 8 feet with alternating steps, with the examiner beside the subject and holding only one of the child's hands, or if he/she achieves a score of 1, which requires the subject to walk 4 to 7 feet with alternating steps, with the examiner beside the subject and holding only one of the child's hands.

For each of these 4 key motor milestones, the numeric score of "2" will be translated into a "mastery," indicating that the child achieved the milestone; the numeric score of "1" will be translated into "emerging", indicating that the child showed emerging skill; a numeric score of "0" or "unscored" equated to "fail," and therefore the subject did not achieve the milestone.

PDMS-2 raw scores will be presented for this study. Normally, the raw scores are transformed relative to the subject's age and measured against what is "normal" for that age. If scores are transformed, all the subjects with AADC deficiency would score markedly below their age range because of their development delays.

The PDMS-2 score sheet is provided in Appendix 1.

7.3.3. Bayley Scale of Infant Development, Third Edition

The Bayley-III is a standardized assessment of cognitive, language, and motor development for children between 1 and 42 months of age. This measure consists of a series of developmental tasks. The Bayley-III has 3 main subscales, which are the Cognitive, Language, and Motor Scales. The Cognitive Scale includes items such as attention to familiar and unfamiliar objects, looking for a fallen object, and pretend play. The Language Scale includes understanding and expression of language, for example, recognition of objects and people, following directions, and naming objects and pictures. The Motor Scale assesses gross and fine motor skills such as grasping, sitting, stacking blocks, and climbing stairs. Only the Cognitive and Language scales from the Bayley-III will be used in this study, as the Bayley-III Motor Scale is largely duplicative of the primary efficacy evaluation (motor milestone achievement using the PDMS-2).

7.3.4. EQ-5D-Y

The EQ-5D-Y is comprehensible instrument suitable for evaluating children and adolescents. The EQ-5D-Y descriptive system comprises the following 5 dimensions: mobility, looking after myself, doing usual activities, having pain or discomfort, and feeling worried, sad, or unhappy. A proxy version of the EQ-5D-Y will be provided by the site and administered by the caregiver. The caregiver will be asked to rate the child's/adolescent's health-related quality of life in the caregiver's opinion.

The EQ-5D-Y will not be administered to subjects under 4 years of age. If the subject turns 4 during the study, the caregiver will complete the EQ-5D-Y per protocol after the subject turns 4.

7.3.5. Body Weight

Many subjects with AADC deficiency are reported to have feeding/swallowing difficulties and failure to thrive or gain weight as appropriate for growth (Wassenberg 2017). Therefore, the change in subjects' body weights over time will be assessed as a supportive, exploratory measure of efficacy.

7.3.6. AADC-Specific Symptoms

Aromatic L-amino acid decarboxylase deficiency is characterized by specific neurological symptoms, including floppiness (hypotonia), oculogyric crisis (OGC) episodes, limb dystonia, and stimulus-provoked dystonia. These symptoms will be evaluated by the investigator as described in Table 1, Table 2, and Table 3.

Detailed neurologic examinations, including assessments of muscle power, muscle tone, and spontaneous movement, will be performed as described in Table 1 and Table 2.

Any OGC episodes and associated concomitant medications will be recorded throughout the Trial Phase and Extension Phase by caregivers using an electronic diary (eDiary) with prespecified questions. In the event that the eDiary cannot be used, a paper version of the diary will be provided. Oculogyric crisis episodes should be entered in the eDiary or paper diary when they occur.

Muscle power will be measured in the following 4 areas: I (right upper extremity), II (left upper extremity), III (right lower extremity), and IV (lower left extremity). Muscle power is typically graded on a 6-point scale as follows:

- 1, no movement
- 2, trace of contraction
- 3, active movement when gravity is eliminated
- 4, active movement against gravity
- 5, active movement against gravity and resistance
- 6, normal strength

7.3.7. Measurement of 3-OMD and 5-HIAA

Similar to L-DOPA, the precursor 5-HTP is decarboxylated by AADC to form serotonin. After action at the nerve synapse, serotonin is reabsorbed into the presynaptic nerve terminal where it can either be repackaged into vesicles or metabolized 5-HIAA. In the presence of AADC deficiency, the 3-OMD level in the CSF is increased and the 5-HIAA level is very low or below the limits of detection due to the abnormally low serotonin production. Upon restoration of AADC activity, concentrations of and 3-OMD levels decrease in the CSF and 5-HIAA rise (Hyland 2006, Hyland 2007).

Neurotransmitter metabolites will be quantified following isocratic, reversed phase high performance liquid chromatography separation and coulometric electrochemical oxidation using EZChrom software.

7.4. Home Care Services

If for unforeseen reasons subjects are unable to travel to the study site, with approval from both the Principal Investigator and PTC medical monitor, they may be offered an opportunity to have study visits performed in their home. This applies to all visits, with the exception of Week 8 (Visit 9), Week 48 (Visit 20), and all visits during the Long-Term Extension Phase which are critical in order to evaluate study endpoints and therefore must occur in the office. In order to conduct the home visits, the subject must agree to utilize home care services. A licensed nurse will then contact the subject to schedule visits. The home care nurse, the home care agency, and the home care services provider may have access to the subject's personal data including their individually identifiable protected health information, such as the subject's name, address, or phone number. This type of information will only be used as necessary to schedule and conduct the home visits and will not be provided to the sponsor.

7.5. Safety Assessments

7.5.1. Peri-Operative Safety Monitoring

Subjects will have preoperative MRI with contrast to rule out any underlying condition that would pose a surgical safety risk or would reveal the subject to be unfit for study inclusion. Surgery will be performed following standard of care, including wound closure techniques and close monitoring of vital signs throughout the surgical procedure. Additionally, monitoring for intraoperative complications and AEs including anesthesia complications, intracerebral hemorrhage demonstrated on imaging during the procedure, CSF leak, hemodynamic instability during the procedure, or equipment malfunction will occur.

Post-surgery, subjects will have monitoring in the ICU for a minimum of one night. Any autonomic dysfunction will be addressed aggressively. Subjects will be monitored on the neurosurgery ward for an additional one to 2 nights prior to discharge. Prior to discharge, subjects will undergo an MRI to evaluate for any evidence of swelling, bleeding, early signs of infection, CSF fistulas or leaks, inflammation, or other possible surgical complications. Subjects will only be discharged if they are tolerating oral intake, have resumed bowel and bladder function, and have good pain control.

Subjects must reside within the vicinity of the hospital where the procedure was performed for a minimum of 7 days following the procedure. Subjects can be seen for an unscheduled visit, if

needed, to assess complications. A second follow-up visit will take place 2 weeks later (ie, 3 weeks after the surgery) to monitor post-surgical recovery, occurrence of AEs, and complete other study procedures.

7.5.2. Adverse Events and Serious Adverse Events

7.5.2.1. Definition of Adverse Events

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not it is considered related to the drug. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease in a study subject who is administered gene therapy in this study.

For this protocol, untoward medical occurrences that should be reported as AEs include the following:

- All AEs during the course of treatment with gene therapy administration.
- All AEs resulting from medication errors such as dispensing or administration error outside of what is described in the protocol.
- Apparently unrelated illnesses, including worsening of a pre-existing illness.
- Injury or accidents. Note that if a medical condition is known to have caused the injury or accident (a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) should be reported as 2 separate AEs. The outcome of the accident (hip fracture secondary to the fall) should be recorded in source documents.
- Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test).
- Laboratory, echocardiogram, or electrocardiogram abnormalities that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they are associated with an already reported clinical event. Laboratory abnormalities associated with a clinical event should be captured in the source documents. Laboratory abnormalities not requiring clinical intervention or further investigation will be captured as part of overall laboratory monitoring and should not be reported as AEs.
- A pre-existing condition (eg, allergic rhinitis) must be noted on the appropriate eCRF at screening but should not be reported as an AE unless the condition worsens, or episodes increase in frequency during the AE reporting period. Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that occurs during the study should be reported as the AE and the resulting appendectomy should be recorded in the source documents and eCRF. If a surgical procedure was planned prior to entry into the study, and the surgery performed is not because of a worsening of a baseline condition, this should not be reported as an AE. Note that, as described in Section7.5.2.2 any hospitalization

occurring as the consequence of an AE during the study period should be reported as an SAE.

Each AE is to be classified as serious or nonserious by the investigator using medical and scientific judgment.

7.5.2.2. Definition of Serious Adverse Events

An SAE is an untoward medical occurrence or effect associated with the use of a gene therapy at any dose, regardless of whether it is considered to be related to the gene therapy, which results in one of the following:

- Results in death. This includes all deaths from time of consent until Final Study Visit, or within 30 days after Final Study Visit, including deaths due to disease progression. Any death occurring later than 30 days following the Final Study Visit need not be reported as an SAE unless it is a result of an event that started within the period covered by the on-study definition. The reported AE should be the event that caused the death. In addition, any AE resulting in death that occurs after the AE reporting period and that the investigator assesses as possibly related to the gene therapy should also be reported as serious.
- Is life-threatening. This refers to an event in which the subject was at risk of death at the time of the event. It does not include an event that, had it occurred in a more severe form, hypothetically might have caused death.
- Requires hospitalization or prolongation of existing hospitalization (excluding hospitalizations for administration of the gene therapy, procedures required by the study protocol, or treatment-related diagnostic procedures; other planned hospitalizations; or hospitalizations related only to progression of disease). Treatments in the emergency room for procedures such as hydration that do not require admitting the subject to the hospital and observational durations in the emergency room for less than 24 hours do not fall into this category.
- Results in persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions.
- Any other medically important event that the investigator or the sponsor judges to be serious or which is defined as serious by the regulatory agency in the local country. These are AEs that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Medical judgment should be exercised in deciding whether an AE is serious based on above definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- A pregnancy resulting in spontaneous abortion, stillbirth, neonatal death, or congenital anomaly (including that in an aborted fetus).

Note that any SAEs occurring within 30 days after the Final Study Visit should be reported to the sponsor if the investigator becomes aware of them.

7.5.3. Adverse Events of Special Interest

Adverse events of special interest (AESIs) will be captured and monitored during this study. Investigators will report all AESIs to PTC Pharmacovigilance, regardless of causality, as described in Section 7.5.8. All AESIs should be reported within 24 hours to the PTC Therapeutics Pharmacovigilance Department on the SAE form. If the event is considered nonserious by the investigator, then the SAE form and AE CRF page should be marked as nonserious.

7.5.3.1. Risks of Neurosurgical Procedure

There are risks associated with neurosurgery, intraputaminal infusion, and use of the cannula, including hemorrhage and infection at the infusion site. Adverse events associated with the neurosurgical procedure and infusion will be documented and reported as AESIs.

Surgical AESIs only need to be recorded as such and reported to Pharmacovigilance when related to the neurosurgical procedure specifically and not when related to general risks of surgery, inclusive of anesthesia-related AEs.

Adverse events that are nonserious and related to general risks of surgery and anesthesia will be recorded as general AEs and will not be reported to PTC Pharmacovigilance. These AEs will be captured as described below in Section 7.5.8.

7.5.3.2. Dyskinesia

Adverse events of dyskinesia have been reported in the clinical studies of eladocagene exuparvovec. Dyskinesia may result from the elevated sensitivity of dopaminergic receptors in AADC-deficient subjects, which may result from chronic severe deficiency of neurotransmitters. After treatment with eladocagene exuparvovec, overstimulation of the dopaminergic receptors may manifest as dyskinesia.

7.5.3.3. Cerebrospinal Fluid Leaks

Cerebrospinal fluid leaks occur when there is a tear or hole in the membranes surrounding the brain or spinal cord, allowing the clear fluid that surrounds and cushions those organs to escape. Because eladocagene exuparvovec will be administered as an intraputaminal infusion, CSF leaks are a potential AE. CSF leaks will be monitored for all subjects intraoperatively and via brain MRI with gadolinium upon discharge and at 3 weeks post-surgery.

7.5.4. Adverse Event Recording

All AEs (both serious and nonserious) that occur in subjects during the AE reporting period (screening until the Final Study Visit) must be recorded, whether or not the event is considered drug related.

All AEs are to be recorded in the source documents and on the eCRF using concise medical terminology; whenever possible, terms contained in the Medical Dictionary for Regulatory Activities (MedDRA) should be employed. In addition, the following information should be recorded:

- Indication of whether the event is serious or nonserious (see Section 7.5.2)
- Relationship to gene therapy (see Section 7.5.5)

- Relationship to surgery
- Severity of the event (see Section 7.5.6)
- Onset date
- Resolution date, or date of death
- Action taken
- Outcome of the event

Classification of the event as serious or nonserious determines the reporting procedures to be followed.

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject/parent(s)/legal guardian/legally acceptable representative. In addition, each study subject/parent(s)/legal guardian/legally acceptable representative will be questioned about AEs at each scheduled clinic visit after gene therapy administration or during any telephone contact with the subject/parent(s)/legal guardian/legally acceptable representative. The type of question asked should be open-ended, for example, "How have you been feeling?" or a similar type of query.

7.5.5. Describing Adverse Event Relationship to Gene Therapy or Surgery

The investigator should provide an assessment of the relationship of the AE to the gene therapy, the cannula, or the neurosurgery (ie, whether there is a reasonable possibility that the gene therapy, the cannula, or the neurosurgery caused the AE) using the considerations outlined in Table 4.

Table 4: Relationship of Gene Therapy to Adverse Event

Relationship	Description
Probable	A clinical event in which a relationship to the gene therapy seems probable because of such factors as consistency with known effects of the drug; a clear temporal association with the use of the drug; lack of alternative explanations for the event.
Possible	A clinical event occurring coincident with administration of the gene therapy and which may or may not be explained by concurrent disease or other drugs or chemicals.
Unlikely	A clinical event with a temporal relationship to the gene therapy exposure that does not preclude causality but for which there is a clear alternate cause that is more likely to have caused the AE than gene therapy. Such alternatives include a concomitantly administered drug, the subject's disease state, other medical conditions, or environmental factors.
Unrelated	A clinical event, for which a relationship to the gene therapy seems improbable because of factors such as inconsistency with known effects of the gene therapy, lack of a temporal association with gene therapy administration, and/or presence of alternative explanations for the event. Alternative explanations might include a known relationship of the AE to a concomitant drug, medical history of a similar event, the subject's disease state, other medical conditions, or environmental factors.

Abbreviations: AE, adverse event

7.5.6. Grading of Severity of Adverse Events

The severity of AE will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. For each episode, the highest severity grade attained should be reported.

If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the AE. For purposes of consistency with the CTCAE, these intensity grades are defined in Table 5.

Table 5: Grading of Adverse Event Severity Grade

Grade	Adjective	Description
1	Mild	Sign or symptom is present, but it is easily tolerated, is not expected to have a clinically significant effect on the subject's overall health and well-being, does not interfere with the subject's usual function, and is not likely to require medical attention
2	Moderate	Sign or symptom causes interference with usual activity or affects clinical status, and may require medical intervention
3	Severe	Sign or symptom is incapacitating or significantly affects clinical status and likely requires medical intervention and/or close follow-up
4	Life-threatening	Sign or symptom results in a potential threat to life
5	Fatal	Sign or symptom results in death

7.5.7. Follow-Up of Unresolved Adverse Events

All AEs should be followed up by the investigator until they are resolved, or the investigator assesses them as chronic or stable. The investigator should consider protocol guidelines and use his/her discretion in ordering additional tests as necessary to monitor the resolution of such events. In the event of additional investigations, the PTC Pharmacovigilance Department or designee should be informed via e-mail or fax. A subject withdrawn from the study because of an AE must be followed by the investigator until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. Follow-up may need to continue after the subject has discontinued from the study, and additional investigations may be requested by the medical monitoring team.

7.5.8. Adverse Event Reporting Period

Investigator site reporting requirements for AEs are summarized in Table 6.

Table 6: Investigator Site Requirements for Reporting Adverse Events

Event	Recorded on the eCRF	Reported to PTC Pharmacovigilance Within 24 Hours of Awareness
Serious AE	All	All
Nonserious AE	All	None
AESIs	All	All
Other, eg, exposure to the gene therapy during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), except occupational exposure	All (regardless of whether associated with an AE)

Abbreviations: AE, adverse event; AESI, adverse event of special interest; eCRF, electronic case report form

The first day of AE reporting will coincide with the date of signing of informed consent and including a minimum of 30 calendar days after the Final Study Visit (Month 60), except as

described in Section 7.5.4. In addition, SAEs occurring in a subject after the study period should be reported to the sponsor if the investigator becomes aware of them.

The medical monitor will review all AEs and SAEs as they are reported from the site. The DSMB will conduct a review of safety data as outlined in the DSMB charter. The DSMB will monitor ongoing safety data to ensure subject well-being, safety, and study integrity.

7.5.9. Serious Adverse Event Reporting

All SAEs should be reported via the SAE report form to PTC within 24 hours of becoming aware of the event(s). In addition, the AE portion of the eCRF must also be completed.

The SAE report form should be signed by the investigator; however, if the investigator is unable to sign at the time of the event or within 24 hours, the form should be signed by the clinical staff member reporting the SAE (eg, the study coordinator). The SAE report form must be faxed or e-mailed to the PTC Pharmacovigilance Department or designee and to the site IRB/IEC (if required by local regulations) within 24 hours.

Follow-up information to the SAE should be clearly documented as "follow-up" in the SAE report form and must also be faxed or e-mailed to the same party. All follow-up SAE report forms for the event must be signed by the investigator. Any source documents (eg, progress notes, nurses' notes, laboratory and diagnostic test results, discharge summaries) provided to the sponsor should be redacted so that the subject's name, address, and other personal identity information are obscured. Only the subject's study number and initials are to be provided (in regions where the provision of such information is permitted). The information in the AE portion of the eCRF and the SAE report form(s) must match or be reconciled. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (for example, if a subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and to document his/her first awareness of the AE.

The PTC Pharmacovigilance Department contact information for reporting SAEs is provided below. This information is also provided in the SAE report form.

PTC Pharmacovigilance Department
E-mail: Pharmacovigilance@ptcbio.com
SAE FAX Line: 1-908-325-0355

7.5.10. PTC Adverse Event Reporting Requirement

As the sponsor of the study, PTC is responsible for reporting certain safety information, particularly SAEs and subject deaths related to participation in the study, to each investigator in an expedited manner. If notification of an AE requiring expedited reporting to investigators is received, PTC or its designated representative will contact each investigational site participating in this study by e-mail, fax, and/or overnight mail such that the investigator can promptly notify the site IRB/IEC per their local requirements. The initial expedited safety report will be provided as required according to local regulations (eg, within 15 days) after the earliest date PTC or an

agent of PTC (eg, a site monitor) becomes aware of an AE. This awareness date is the date the regulatory reporting clock begins, and the date is considered Day 0.

7.5.11. Other Safety Assessments

Other safety assessments will include laboratory assessments (complete blood count with differential and platelets, chemistry, and coagulation), physical examinations, vital signs, and height and weight. These assessments will be performed as detailed in Table 1,Table 2, and Table 3.

Viral shedding will be assessed in blood, CSF, and urine as per the Schedule of Events to identify any possible risk of exposure to those who come into contact with a study subject. Anti-AAV2 Antibody testing and T-cell sample collection will be performed as per the Schedule of Events to assess the immune response to gene therapy.

7.5.12. Safety Assessment Committee

The DSMB will evaluate all AEs, SAEs, and AESIs.

8. STATISTICAL METHODS AND DATA ANALYSIS

8.1. Sample Size Determination

This study has no formal statistical hypothesis testing, and the sample size is not based on statistical consideration. A minimum of 3 subjects is planned to assess HVA level at Week 8 and safety of the SmartFlow MR-compatible ventricular cannula for administering eladocagene exuparvovec to pediatric subjects.

8.2. Subject Population(s) for Analysis

The following analysis population will be defined for the study:

Pharmacodynamic (PD) population: The PD population will consist of all subjects enrolled in the study who have received any amount of the study drug and have both baseline and at least one post-baseline value of at least one PD variable.

Safety Population: The safety population will consist of all subjects enrolled in the study who have received any amount of study drug.

Efficacy Population: The efficacy population will consist of all subjects enrolled in the study who have received any amount of the study drug and have both baseline and at least one post-baseline evaluation of at least one efficacy variable.

All analyses of PD variables will be based on the PD population. Evaluation of the safety variables will be based on the safety population, and all efficacy summary and analyses will be based on the efficacy population.

8.3. General Approach

Summaries for PD, safety, and efficacy will be provided from time of gene therapy administration until the end of the follow-up. If needed, summaries will be provided for PD, safety and, if appropriate, efficacy variables at a timepoint that matches the agreement with the health authority.

Study baseline for a variable is defined as the last non-missing data collected prior to treatment. If a separate set of summaries is needed for the Long-Term Extension Phase, baseline for the Long-Term Extension Phase is defined as the last non-missing data collected prior to the Long-Term Extension Phase.

8.3.1. Subject Disposition and Characteristics

Subject disposition, demographics, and baseline characteristics will be summarized. Reasons for study discontinuation and time of withdrawal from study will be described.

8.3.2. Analysis of Primary Endpoints

8.3.2.1. Primary Efficacy Analysis

Observed values and change from baseline in HVA at Week 8 will be summarized using descriptive statistics (count, mean, standard deviation, median, minimum, and maximum) for each timepoint.

8.3.2.2. Primary Safety Analysis

The primary safety analysis will focus on TEAEs that are defined as AEs with a start date after or worsen after receiving eladocagene exuparvovec.

The time of gene therapy administration will be the start time of the first infusion. All AEs reported will be coded using MedDRA. The number and proportion of subjects reporting TEAE will be summarized by System Organ Class (SOC) and by Preferred Term (PT) within SOC. Summaries will also be provided for each severity grade, relationship to cannula device, to gene therapy, and to neurosurgical procedure, and AEs of special interest.

Serious Adverse Events will be summarized using SOC and PT.

8.3.3. Analysis of Secondary Endpoints

Observed values and change from baseline in the neurotransmitter CSF metabolites HVA, 5-HIAA, 3-OMD in CSF; brain ^{18}F-DOPA PET; PDMS-2 total and subscale scores; Bayley-III cognitive and total language subscale scores; EQ-5D-Y scores; body weight; and AADC-specific symptoms will be summarized using descriptive statistics (count, mean, standard deviation, median, minimum, and maximum) or proportion as appropriate for each timepoint.

The number and percentage of subjects who achieve each motor milestone will be summarized by timepoint.

Oculogyric crisis diary data will be summarized by severity, frequency, and proportion and duration of time subjects experienced OGC during the study for selected timepoints, as appropriate.

Respiratory infection rate will be summarized over time.

TEAEs will be summarized as described in Section 8.3.2. The number of subjects who experience dyskinesia, number of dyskinesia episodes, median time to first episode, and summary statistics for duration of dyskinesia events will be provided.

Physical examination, vital signs, MRI, clinical laboratory values, T-cell, anti-AAV2 antibody values, and viral shedding will be summarized by visit, and shift table(s) will be provided if appropriate.

8.3.4. Planned Interim Analysis

No interim analysis is planned for this study.

9. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

9.1. Regulatory, Ethical, and Study Oversight Considerations

9.1.1. Informed Consent Process

By signing the protocol, the investigator assures that informed consent will be obtained from each subject/subject's caregiver prior to study entry and that the informed consent will be obtained in accordance with current regulations.

The investigator or sub-investigator will give each subject/subject's caregiver full and adequate verbal and written information regarding the objectives and procedures of the study and the possible risks involved. An informed consent document will be provided to each subject/subject's caregiver in a language in which they are fluent. This information must be provided to the subject/subject's caregiver prior to undertaking any study-related procedure. Adequate time should be provided for the subject/subject's caregiver to read the informed consent, to understand the risks and benefits of participating in the study, and to ask any questions that the subject may have about the study. The subject/subject's caregiver should be able to ask additional questions as and when needed during the conduct of the study. The subject's caregivers' signature on the informed consent form (ICF) should be obtained at the investigator site in the presence of the investigator or a qualified representative (eg, sub-investigator).

Each subject/subject's caregiver will be given a copy of the signed consent form. The original signed ICFs will be retained by the investigator with the study records.

The written subject information must not be changed without prior approval by PTC and the IRB/IEC.

9.1.2. Study Discontinuation and Closure

PTC reserves the right to discontinue the study prior to inclusion of the intended number of subjects. The investigator, after consultation with the PTC medical monitor, reserves the right to discontinue the study at the investigator site for safety reasons at any time.

After a decision to terminate the study, investigators must contact all subjects who are continuing their participation in the study and must do so within a period set by PTC. As directed by PTC, all study materials must be collected, and all electronic data entry forms completed to the greatest extent possible.

9.1.3. Confidentiality and Privacy

Research records will be collected and stored in a manner that protects the confidentiality of subject information. The names and identities of all research subjects will be kept in strict confidence and will not appear on eCRFs, paper case report forms, or other records provided to or retained by PTC (or its authorized designee). The names and identities of the subjects need not be divulged; however, the records must nevertheless be inspected. This will be accomplished by redacting the subject's name and replacing the name with the subject's study identification number on any record provided to or retained by PTC. The ICF must include appropriate statements explaining these requirements.

By signing this protocol, the investigator affirms to PTC that the investigator will maintain, in confidence, information furnished by PTC and will divulge such information to the IRB/IEC under an appropriate understanding of confidentiality with such board.

9.1.4. Future Use of Stored Specimens and Data

As part of the current study, biomarker data will be collected from all subjects.

Processing of genetic, anti-AAV2 antibody, CSF neurotransmitter, and AADC enzyme samples will be performed by central laboratories under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of the sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The sponsor will not sell the samples to a third party.

All samples, with the exception of those collected for anti-AAV2 antibody testing, will be stored until the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, those samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed. The samples collected for anti-AAV2 antibody testing will be stored for potential future testing. No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with any of the biologic samples. All samples will be single coded. The sponsor will take steps to ensure that data are protected accordingly, and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- Contract Research Organizations (CROs) retained by the sponsor
- IECs or IRBs that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report which can include part or all the coded data, in listing or summary format. Other publication (eg, in peer-reviewed scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

9.1.5. Safety Oversight

Safety will be monitored on a regular basis by the sponsor's medical monitor. To protect subjects' safety, an independent DSMB, which will include a pediatric neurosurgeon and a pediatric neurologist, will be established to monitor the ongoing safety data during the Trial Phase. Full details of the DSMB procedures, including primary responsibilities of the DSMB, its relationship with other study components, its membership, and its purpose and timings of its meetings, will be documented in a DSMB charter. These details will also include procedures to ensure confidentiality and proper communication, the guidelines to be implemented by the DSMB, and an outline of the content of the reports that will be provided to the DSMB.

The DSMB will conduct a review of safety data as outlined in the DSMB charter. Review meetings will allow for the appropriate monitoring of safety related to the surgical procedure with the SmartFlow MR-compatible ventricular cannula. Review by DSMB will not be required in order to enroll successive subjects. The DSMB will monitor ongoing safety data to ensure subject well-being, safety, and study integrity.

The DSMB may review the safety data at other times as warranted by emerging results. Based on review of the safety data, the DSMB can recommend continuation of the study unchanged, study interruption, study termination, modification of the trial, or alteration in the DSMB monitoring plan. Further information regarding the DSMB review process is provided in the DSMB charter.

9.1.6. Clinical Monitoring

In accordance with 21 Code of Federal Regulations Part 312.56 and/or relevant ICH guidelines, PTC or a designee will periodically inspect all eCRFs, study documents, research facilities, and clinical laboratory facilities associated with this study at mutually convenient times, before, during, and after completion of the study. As required by applicable regulations (Responsibilities of sponsors and investigators), the monitoring visits provide PTC with the opportunity to evaluate the progress of the study; verify the accuracy and completeness of data in the eCRFs; ensure that all protocol requirements, relevant regulations, and investigator's obligations are being fulfilled; and resolve any inconsistencies in the study records. This includes inspection of all documents and records required to be maintained by the investigator, including but not limited to medical records (office, clinic, or hospital) for the subjects in this study. The names and identities of all research subjects will be kept in strict confidence and will not appear on eCRFs or other records retained by PTC. The investigator/institution guarantees direct access to source documents by PTC and appropriate regulatory authorities.

It is important that the investigator and relevant institutional personnel are available during the monitoring visits and possible audits or inspections and that enough time is devoted to the process.

9.1.7. Quality Assurance and Quality Control

To ensure compliance with GCP and all applicable regulatory requirements, PTC, PTC's representatives, a regulatory authority, or an IRB may conduct a quality assurance audit. Reasons for quality assurance audit may include but are not limited to random selection, geographic proximity, suspected GCP violation, recurring protocol deviations, etc. The purpose of a sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. The investigator should contact the sponsor immediately if contacted by a regulatory agency about an inspection.

9.1.8. Data Handling and Record Keeping

To enable evaluations and/or audits from regulatory authorities or PTC, the investigator agrees to keep accurate and complete records, including the identity of all participating subjects (sufficient information to link eCRFs and clinic records/source documents), all original signed ICFs, electronic copies (ie, CD-ROM, USB, etc.) or paper copies of the data that have been captured in the electronic data capture for each subject (eCRFs), and detailed records of gene therapy disposition. All records and documents pertaining to the study will be maintained by the investigator until notification is received from PTC that the records no longer need to be retained.

The investigator must obtain written permission from PTC before disposing of any records. The investigator will promptly notify PTC in the event of accidental loss or destruction of any study records. If the investigator relocates, retires, or for any reason withdraws from the study, the study records may be transferred to an acceptable designee, such as another investigator, another institution, or to PTC as applicable.

9.1.9. Protocol Deviations

A protocol deviation is defined as any intentional or unintentional change to, or noncompliance with, the approved protocol procedures or requirements. Deviations may result from the action or inaction of the subject, investigator, or site staff. Examples of deviations include, but are not limited to:

- Failure to adhere to study exclusion and inclusion criteria
- Failure to comply with dispensing or dosing requirements
- Use of medications that are specifically prohibited in the protocol
- Missed or out-of-window visits
- Drug dosing not administered within the time frame specified in the protocol
- Failure to adhere to test requirements, including vital signs, laboratory tests, physical examinations, medical history, etc. (either tests not done, incorrect tests done, or not done within the time frame specified in the protocol)
- Procedural deviations such as incorrect storage of gene therapy, failure to update the ICF when new risks become known, or failure to obtain IRB approvals for the protocol and ICF revisions

Major deviations are any deviations that impact subject eligibility (ie, protocol inclusion/exclusion violations), subject safety, or a subject's ability to continue in the clinical study.

At the outset of the study, a process for defining and handling protocol deviations will be established with the CRO. This will include determining which deviations will be designated major; thus, requiring immediate notification to the PTC medical monitor and the sponsor.

Prospective deviations (eg, protocol waivers) are prohibited per PTC policy.

The investigator is responsible for seeing that any known protocol deviations are recorded and handled as agreed.

9.1.10. Publication and Data Sharing Policy

The information developed during the conduct of this clinical study is considered confidential by PTC. This information may be disclosed as deemed necessary by PTC.

PTC intends that the data from this study will be presented and published. The PTC staff in collaboration with the investigator will be responsible for writing presentations and manuscripts for publication. Investigators will not be allowed to publish or present the data from this study without prior agreement with PTC.

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the Clinical Study Site Agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

Data from the study will be pooled and analyzed by the sponsor or the sponsor's designee. If a publication is not forthcoming within 12 months of completion of the study, the investigator may publish or present the results generated by the study.

The investigator will provide the sponsor with a copy of any proposed publication or presentation for review and comment at least 60 days prior to such presentation or submission for publication. The sponsor shall inform the investigator in writing of any changes or deletions in such presentation or publication required to protect the sponsor's confidential and proprietary technical information and to address inaccurate data or inappropriate interpretations in the context of any pooled multicenter results. At the expiration of such 60-day period, the investigator may proceed with the presentation or submission for publication unless the sponsor has notified the institution or the investigator in writing that such proposed publication or presentation discloses the sponsor's confidential and proprietary technical information. Further,

upon the request of the sponsor, the investigator will delay the publication or presentation for an additional 90 days to permit the sponsor to take necessary actions to protect its intellectual property interests.

9.1.11. Additional Considerations

Not applicable.

10. PROTOCOL AMENDMENT HISTORY

Version 1.0: 25 February 2020

Version 1.1: 24 March 2020

Version 2.0: 17 July 2020

Version 3.0: 17 August 2020

Version 4.0: 24 November 2020

Version 5.0: 21 April 2021

Version 6.0: 16 August 2021

Version 7.0: 11 November 2021

Version 8.0: 22 March 2022

Version 9.0: 20 July 2022

Version 10.0: 28 April 2023

Version 11.0: 01 September 2023

10.1. Version 1.1: 24 March 2020

Overall reason for Version 1.1: The overall reason for this amendment was to incorporate feedback from FDA.

Item No.	Protocol Section	Amendment/Update	Reason/ Rationale
1	Protocol	Document date/version and abbreviations were updated; small grammatical and format changes were made throughout. Added pediatric to characterize study population.	Update
2	Synopsis, 2.3.2, 7.4, 8.3.4	Changed section to Exploratory Endpoints, and deleted AIMS, Bayley Scale of Infant Development, Gross Motor Function Measure, and Manual Ability Classification System.	Agency request
3	3.1	Added an interval of 3 weeks between successive subjects.	Agency request
4	Synopsis, 3.1, 7.1	Changed Part A and Part B to Trial Phase and Extension Phase.	Update
5	Synopsis, 4.1	Deleted former Inclusion Criterion 2, added new inclusion criteria for age, cranium development, lack of benefit from standard medical therapy, unable to ambulate independently, and laboratory values within normal pediatric range.	Agency request
6	5.3	Allow treatments for AADC deficiency throughout study duration as long as prespecified conditions are met.	Agency request
7	6.1	Added stopping rules.	Agency request
8	7.1	• Clarified hospitalization stay. • Specified that PDMS-2 should be done at same time of day at baseline, 6 months, 12 months. • Deleted AIMS, Bayley Scale of Infant Development, Gross Motor Function Measure, and Manual Ability Classification System.	Agency request
9	7.5.1	Added peri-operative safety monitoring measures.	Agency request

Item No.	Protocol Section	Amendment/Update	Reason/ Rationale
10	7.5.2.2	Deleted sentence that an event need not be reported as an SAE if it exclusively represents a relapse of an expected change or progression.	Agency request
11	7.5.12	Added an independent pediatric neurologist to evaluate safety.	Agency request
12	Attachment 1	Added PDMS-2 score sheet.	Agency request

10.2. Version 2.0: 17 July 2020

Overall reason for Version 2: The overall reason for this amendment was to address feedback from FDA.

Item No.	Protocol Section	Amendment/Update	Reason/ Rationale
1	Protocol	Document date/version and abbreviations were updated; minor grammatical, format changes, and clarifications were made throughout. The Study Visits were changed from months to weeks. The Summary of Events was split into 2 tables and the other tables in the document were renumbered. The visits/assessments in the new Summary of Events table reporting the Extension Phase (the new Table 2) were revised to streamline the in-clinic visits.	Update
2	Synopsis	For clarity, text was added regarding the number of subjects to be enrolled. Details pertaining to DSMB safety monitoring were added. Inclusion criteria #1 and #2 and exclusion criteria #5 were modified for clarity. Text regarding metal was added to exclusion criteria #3. Inclusion and Exclusion Criteria were added to explain criteria regarding pregnancy and breastfeeding. Brain ^{18}F-DOPA PET was added as an Other Exploratory Endpoint.	Update
3	Protocol Identifiers and Study Personnel	The “P” from the IND number was deleted as it is not applicable.	Update
3	2.3.2, 8.3.4	Brain ^{18}F-DOPA PET was added as an Other Exploratory Endpoint.	Update
4	3.1, 8.1	For clarity, text was added regarding the number of subjects to be enrolled.	Update
5	3.1	Details pertaining to DSMB safety monitoring were added. The length of the study was changed from “13 months” to “54 weeks”.	Update
6	3.2	Text regarding the relative average mass of a child brain versus the adult brain has been deleted. Text regarding infusion was modified to be consistent with the Surgical Manual.	Update
7	4.1	Inclusion criteria #1 and #2 were modified for clarity. Inclusion criteria were added to explain criteria regarding pregnancy.	Update

Item No.	Protocol Section	Amendment/Update	Reason/ Rationale
8	4.2	Text regarding metal was added to exclusion criteria #3. Exclusion criteria #5 was modified for clarity. Exclusion criteria was added to explain criteria regarding pregnancy and breastfeeding.	Update
9	5.1	Text regarding infusion was modified to be consistent with the Surgical Manual.	Update
10	5.2.2	IP storage conditions revised from "-80°C" to "≤-65°C."	Update
11	5.3	For clarity, "dosage has been stable for a minimum of 6 months" has been deleted from the list of requirements for the medications related to the treatment of AADC deficiency.	Update
12	6.1	Stopping rules were updated.	Agency request
13	6.2	Text regarding withdrawal of consent was modified for clarity.	Update
14	7.1	The study days for screening was changed. Brain MRI with gadolinium to assess for CSF leakage/fistula or signs of inflammation was added upon discharge and at 3 weeks post-surgery. Collecting CSF history and genetic testing were added as assessments. Visits were modified for CSF neurotransmitter analysis, Brain MRI, Brain CT, 24-hour Holter Monitor, laboratory tests, and PDMS-2. Definitions for a complete physical and targeted physical examinations were added. Text added to the MRI sequencing as clarification. Phone visits were added for AE assessments. Text to state "with gadolinium" was added to footnotes regarding MRIs. Footnotes regarding analysis by a central lab and admitting subjects to the hospital at the discretion of the PI were added.	Update and Agency request
15	7.3	Text stating that PET imaging will be analyzed by a central reader was added.	Update
16	7.4.4	Details regarding untreated CSF samples and metabolites was deleted since the details are not needed for a protocol.	Update
17	7.5.1	Text was added to clarify wound closure techniques. Text regarding assessing complications, if needed, was modified.	Agency request/Update
18	7.5.3.3	Brain MRI with gadolinium to assess for CSF leakage/fistula or signs of inflammation was added upon discharge and at 3 weeks post-surgery.	Agency request
19	7.5.5	Text regarding withdrawal and rechallenge of study drug was deleted from Table 2 since this is a single-dose study.	Update
20	7.5.8	AEs of Special Interest were added to Table 4.	Update
21	7.5.8, 7.5.12, 9.1.5	Details pertaining to DSMB safety monitoring were added.	Agency request
22	9.1.4	For clarity, text regarding processing samples and storage was modified. Paragraph regarding biomarker analysis was deleted as this is no longer applicable to this study.	Update
23	9.1.9, 9.1.10	Text updated to current PTC terminology.	Update

10.3. Version 3.0: 17 August 2020

Overall reason for Version 3.0: To update the protocol based on the assessments and analysis that will conducted during the study.

Item No.	Protocol Section	Amendment/Update	Reason/ Rationale
1	Protocol	Document date/version and abbreviations were updated; minor grammatical, format changes, and clarifications were made throughout.	Update
2	Synopsis	The Inclusion criteria was modified to clarify the genetic testing and enzyme activity is required. Also, the Inclusion criteria was modified to take out the CSF history as it will not be required for inclusion. The Statistical Methods section was updated for clarity and to add text regarding the analysis for the Extension Phase.	Update
3	2.3.1	Corrected “54 weeks” to “48 weeks”. “24-hour Holter Monitor” will not be assessed. Therefore, the assessment has been deleted from the protocol.	Update
4	4.1	The Inclusion criteria was modified to clarify the genetic testing and enzyme activity is required. Also, the Inclusion criteria was modified to take out the CSF history as it will not be required for inclusion.	Update
5	7.1 (Schedule of Events for the Trial Phase and the Extension Phase)	Rows to report the type of visit were added. Viral Shedding was added as an assessment. The rows reporting the eDiary for Oculogyric crisis were modified. “24-hour Holter Monitor” will not be assessed. Therefore, the assessment has been deleted from the protocol. Oculogyric crisis removed from Table 2 (the Extension Phase table). Dosing Day (D1) was added as a visit for “Brain MRI (T1-MPRAGE and T2-FLAIR sequences).” A row for “Real-time intrasurgical MRI” was added. Pregnancy Serum βHCG Test was added as an assessment during the Extension Phase. The rows for “AEs” and “AE phone visit” were combined into one row. Footnotes were updated for clarity, based on what will be assessed, and/or for consistency with the changes made to the tables.	Update
6	7.4.3	Text regarding the eDiary was added for clarity.	Update
7	7.5.11	“24-hour Holter Monitor” will not be assessed. Therefore, the assessment has been deleted from the protocol. Viral Shedding was added as an assessment.	Update
8	8.1	The statement regarding sample size was replaced with “This study has no formal statistical hypothesis testing.”	Update
9	8.3	Text was added to clarify the baseline definition for a variable.	Update
10	8.3.1	Statement regarding subject characteristics at study entry was deleted.	Update
11	8.3.2	Definition of when a TEAE should be recorded was clarified.	Update
12	8.3.4	Text was added to describe the analysis for OGC data.	Update
13	9.1.5	Text regarding the timing for the DSMB monitoring were added.	Update

10.4. Version 4.0: 24 November 2020

Overall reason for Version 4.0: To update study assessments and revise the Schedule of Events.

Item No.	Protocol Section	Amendment/Update	Reason/ Rationale
1	Protocol	Document date/version and abbreviations were updated; minor grammatical, format changes, and clarifications were made throughout.	Update
2	5.3	Language prohibiting the use of blood thinners 7 days prior to surgery was added.	Update
3	7.1 (Schedule of Events)	The visit windows for the Screening Visit and Baseline Visit were updated to Week -6 to Week -2 and ±3 days, respectively.	Update
4	7.1 (Schedule of Events)	Footnotes in the Schedule of Events were revised and updated.	Update
5	7.1 (Schedule of Events for the Trial Phase)	5-HTP was added to footnote e.	Update
6	7.1 (Schedule of Events for the Trial Phase)	Footnote “h” describing collection of CSF for analysis of viral shedding during the surgical procedure was added.	Update
7	7.1 (Schedule of Events for the Trial Phase)	The predose brain CT scan was removed.	Update
	7.1 (Schedule of Events for the Trial Phase)	Laboratory tests were added to the Screening Visit in the Schedule of Events for the Trial Phase.	Update
8	7.5	Language describing a home care services option was added.	Update

10.5. Version 5.0: 21 April 2021

Overall reason for Version 5.0: To revise the timing of DSMB review of subject safety data.

Protocol Section	Amendment/Update	Reason/Rationale
Protocol	Document date/version and abbreviations were updated; minor grammatical changes, format changes, and clarifications were made throughout.	Update.
Protocol Identifiers and Study Personnel	Study personnel were updated.	Update.
Synopsis, Section 3.1, Section 7.5.8, Section 9.1.5	The time period for DSMB review of subject safety data was updated to 3 weeks after the first and third subjects are dosed, and 3 weeks after every third subject is dosed, thereafter. Additionally, language describing the formal review of AE data to the DSMB was updated to 2 weeks after the first subject is dosed.	Update.
Synopsis, Section 3.1, Section 7.5.8, Section 9.1.5	A statement to clarify that DSMB review is not required to enroll successive subjects was added.	Update.

Protocol Section	Amendment/Update	Reason/Rationale
Synopsis, Section 3.1	The interval of at least 4 weeks between dosing subjects was removed.	The removal of mandatory wait time between subjects is supported by the safety of drug product, as demonstrated by the 28 subjects treated in the eladocagene exuparvovec trials conducted in Taiwan, and the safety of the drug product and the SmartFlow cannula, as demonstrated by 2 subjects in the French Temporary Use Authorization (ATU) study.
Section 3.1	Information about the option for subjects to roll into a long-term follow-up study was added.	Update.
Synopsis, Section 3.1	Revised Inclusion Criterion 1 to include subjects with "genetically confirmed AADC deficiency with typical clinical characteristics" and deleted "confirmed diagnosis of AADC deficiency confirmed by compound heterozygous or homozygous pathogenic variants in the *DDC* gene."	Update.
Section 4.1, Section 7.1	An inclusion criterion stating that subjects must test negative for COVID-19 a maximum of 72 hours prior to gene therapy administration was added. If a subject tests positive for COVID-19 at the Screening or Baseline Visit, he/she will need to have negative test results for 2 weeks (2 weeks since the last positive test result and 2 negative test results a minimum of 14 days apart, with the second negative test result no more than 72 hours prior to surgery) before receiving gene therapy. This requirement was included in the Letter of Clarification #3, dated 11 January 2021, and the criterion added to the protocol covers all requirements stated in the Letter of Clarification (ie, that a subject tests negative prior to receiving gene therapy).	Update.
Section 4.3	Rescreening language was revised to include subjects who test positive for COVID-19.	Update.
Section 5.4	Language describing the permissibility of COVID-19 vaccines as concomitant therapy was added.	Update.
Section 5.5	A new section, Organ Donation, was added to provide guidance about donation of organs, tissues, blood, and body fluids during and after the study.	Update.
Section 6.1	The occurrence of any significant procedural deviation or violations (eg, dosing error or equipment failure) was removed from the list of events that would lead to halting of study enrollment.	Update.

Protocol Section	Amendment/Update	Reason/Rationale
Section 7.1	The baseline MRI assessment (T1-MPRAGE and T2-FLAIR sequences) was removed from the Schedule of Events for the Trial Phase.	The assessment was removed to streamline and simplify the Screening and Baseline Visits, and to limit the subjects' exposure to sedation.
Section 7.1	A footnote was added to describe flexibility around the Screening Visit window if there are unforeseen circumstances that impact the subject's ability to adhere to the window.	Update.
Section 7.1	COVID-19 testing was added to the Baseline Visit. A footnote explaining that the subject must test negative for COVID-19 a maximum of 72 hours before receiving gene therapy was added. If a subject tests positive for COVID-19 at the Screening or Baseline Visit, he/she will need to have negative test results for 2 weeks (2 weeks since the last positive test result and 2 negative test results a minimum of 14 days apart, with the second negative test result no more than 72 hours prior to surgery) before receiving gene therapy.	Update.
Section 7.1	Pregnancy testing was added to Dosing Day (D1) and removed from Discharge Day (Day 3).	Update.
Section 7.1	βHCG was removed from the required pregnancy test.	Update.
Section 7.1	Pregnancy testing was added to the Week 12 and Week 36 visits.	Update.
Section 7.1	Lumbar puncture was added to footnote n in Table 1 and footnote g in Table 2.	Update.
Section 7.1	Footnote r for Table 1 was updated to include "for each OGC occurrence".	Update.

10.6. Version 6.0: 16 August 2021

Overall reason for Version 6.0: To update the study stopping rules and Schedule of Events.

Protocol Section	Amendment/Update	Reason/Rationale
Protocol	Document date/version and abbreviations were updated; minor grammatical changes, format changes, and clarifications were made throughout.	Update.
Section 1.2	Information for the ongoing clinical Studies AADC-010 and AADC-011 was updated.	Update.
Synopsis, Section 2	Language describing the primary objective was revised for clarity. No change to the primary objective was made.	Update.
Synopsis, Section 2	The Bayley-III and EQ-5D-5L were added as other exploratory endpoints.	Update.
Synopsis, Section 3.1, Section 7.5.8, Section 9.1.5	The timing of DSMB reviews was revised to at least 3 weeks after the first subject is dosed, at least 3 weeks after the third subject is dosed, and at least 3 weeks after every third subject thereafter is dosed.	Update.

Protocol Section	Amendment/Update	Reason/Rationale
Section 3.1, Section 7.1	The Screening Window was extended from -6 to -2 weeks prior to dosing to -10 to -2 weeks prior to dosing. The total length of study, including the Screening Window, is now 58 weeks. The footnote describing the Screening Window was updated.	Update.
Section 3.1	Details pertaining to the length of the long-term follow-up study were updated.	Update.
Section 6.1	The subject-level and study-level stopping rules were updated to include presence of a clinically significant CSF leak, in the opinion of the investigator.	Update.
Section 7.1	A COVID-19 test was added to the Schedule of Events for the Trial Phase at Dosing Day.	Update.
Section 7.1	A footnote clarifying that P-A and lateral chest x-rays will be performed was added.	Update.
Section 7.1	Text clarifying that the CMP portion of the laboratory test will include total bilirubin was added to the Schedule of Events for the Trial Phase and the Extension Phase.	Update.
Section 7.1, Section 7.5.1.1	T-cell sample collection was added to the Schedule of Events at Screening, Dosing Day, Visit 4, Visit 6, Visit 9, Visit 11, Visit 14, Visit 17, and Visit 20.	Update.
Section 7.1	Details pertaining to collection of urine for viral shedding assessments were added in a footnote to the Schedule of Events for the Trial Phase and the Extension Phase.	Update.
Section 7.1	Activated partial thromboplastin time (aPTT) was added to the list of coagulation tests in the laboratory tests in the Schedule of Events for the Trial Phase and the Extension Phase.	Update.
Section 7.1, Section 7.3	A statement about Bioclinica performing central reads on PET scans was added.	Update.
Section 7.1, Section 7.3.3	The Bayley-III assessment was added to the Schedule of Events at Baseline, Visit 14, and Visit 20, and a description of the assessment was added.	Update.
Section 7.1, Section 7.3.4	The EQ-5D-5L was added to the Schedule of Events at Baseline, Visit 14, and Visit 20, and a description of the assessment was added.	Update.
Section 7.5.3.1	Language related to reporting AESIs related to the neurosurgical procedure to PTC Pharmacovigilance was revised to capture events specific to the neurosurgical procedure and not general risks associated with surgery. Other AEs that may occur during the surgical procedure will be captured as general AEs as described in Section 7.6.8.	This language was updated to ensure that risks associated specifically with the neurosurgical procedure are reported to PTC Pharmacovigilance.
Section 8.3	The General Approach section of the Statistical Methods and Data Analysis was updated to reflect changes to study assessments (Bayley-III, EQ-5D-5L, and body weight) in this amendment. Other revisions were made for clarity.	Update.

10.7. Version 7.0: 11 November 2021

Overall reason for Version7.0: To update the protocol to align with administrative letters and assessment updates.

Protocol Section	Amendment/Update	Reason/ Rationale
Protocol	Document date/version were updated, and minor typographical/formatting changes were made.	Update.
Synopsis	The length of time for the long-term follow-up study was updated to 10 years for consistency with the rest of the document.	Update.
Synopsis, Section 2.3.2, Section 7.1, Section 7.3.4, Section 8.3.4	The EQ-5D-5L assessment was changed to the EQ-5D-Y assessment for subjects in the study.	Update.
Synopsis, Section 3.1, Section 7.5.8, Section 9.1.5	The language describing the timing of DSMB reviews and general information about DSMB reviews was revised.	Update.
Section 1.2	Description of completed clinical Study AADC-010 was updated.	Update.
Synopsis, Section 4.1	The new inclusion criterion #8 was added: Subject must be on stable dosage for 3 months prior to baseline for all medications related to treatment of AADC deficiency, including dopamine agonists, monoamine oxidase inhibitors, anticholinergic drugs, and vitamin B6.	Update.
Section 5.3.4	The formulation, appearance, packaging, and labeling section was updated to align with the most recent IB and Chemistry, Manufacturing and Controls module documents.	Update.
Section 6.1	Language to include applicable country health authorities was added.	Update.
Section 7.1	Footnote a in the Schedule of Events for the Trial Phase was updated to include which Screening assessments (local laboratory assessments, physical examination, and vital signs) need to be repeated if the Baseline Visit does not occur within 9 weeks after the Screening Visit per the Screening Window.	Update.
Section 7.1	Footnote c in the Schedule of Events for the Trial Phase were revised for clarity.	Update.
Section 7.1	Footnote d in the Schedule of Events for the Trial Phase was added to provide exemption from genetic testing in cases where subjects have available genetic enzyme testing results.	Update.
Section 7.1, Section 7.3.6	Language describing the OGC eDiary was revised and updated to describe both an eDiary and a paper diary and to include that in the event that the eDiary cannot be used, a paper diary will be provided.	Update.
Section 7.3.2	A description of the motor achievement for a score of 1 for each of the motor milestones was added. The language describing the scores of “1” and “2” for PDMS-2 skill items was revised such that scores of “1” are defined as achieving an emerging skill and scores of “2” are defined as mastery of the skill to align with how PDMS-2 subject data are analyzed.	Update.
Section 7.5.3, Section 7.5.3.1	Instructions for reporting AESIs using the SAE form and clarification about reporting AESIs related specifically to the neurosurgical procedure were added.	Update.

10.8. Version 8.0: 22 March 2022

Overall reason for Version 8.0: To add the optional Long-Term Extension Phase of the study to the protocol and to update to align with procedural clarifications.

Protocol Section	Amendment/Update	Reason/ Rationale
Protocol	The version number and date were updated throughout. Editorial and administrative revisions (eg, typographical error, punctuation, tenses, abbreviations) were incorporated to provide clarity. The synopsis and Schedule of Events were updated to be consistent with changes in the protocol.	Update.
Protocol Identifiers and Study Personnel	Study personnel were updated.	Update.
Section 1.2	The duration of Study 011 was updated to 13 months.	Update.
Section 3.1, Section 3.3	The protocol was amended to include an optional Long-Term Extension Phase in order to capture long-term safety and efficacy data for subjects treated in the Trial Phase and Extension Phase.	Update.
Section 4.1	Inclusion criterion 11 was updated for consistency with inclusion criterion 12. The words “with custody” were added to the criterion.	Update.
Section 4.3	Language related to rescreening for subjects who withdraw consent prior to dosing was added.	Update.
Section 7.1	Footnote a was added to the Schedule of Events for all Phases to allow flexibility for timing of study visits.	Update.
Section 7.1	A footnote was added to the to the Schedule of Events for all phases of the study to specify the age requirement for administering the EQ-5D-Y.	Update.
Section 7.1	Text was added to the footnote pertaining to COVID-19 testing in the Schedule of Events for the Trial Phase. The requirement for pre-consent and a negative test prior to the Screening Visit was added.	Update.
Section 7.1, Section 7.3	The vendor name (Bioclinica) was removed from the PET footnotes in the Schedule of Events for the Trial Phase and Extension Phase and from the description of the PET scans in Section 7.3.	Update.
Section 7.1	Footnote l was deleted for the CSF neurotransmitter and viral shedding (CSF) assessment on the day of surgery in the Schedule of Events for the Trial Phase as the timing of the assessment is captured in footnote m.	Clarification.
Section 8	The Statistical Methods and Data Analysis Section was updated to include information about the optional Long-Term Extension Phase. Edits were also made for clarity in General Approach, and Analysis of Safety Endpoints.	Update.

10.9. Version 9.0: 20 July 2022

Overall reason for Version 9.0: To update the protocol to align with administrative letters and procedural updates.

Protocol Section	Amendment/Update	Reason/ Rationale
Protocol	The version number and date were updated throughout.	Update.
Section 7.1	Footnote o in Table 1 and footnote i in Table 2 were updated in the Schedule of Events to allow for an additional day of flexibility for timing of study visits and to add clinical assessment details.	Update.
Section 7.3	Language regarding the PET tracer dose was updated to align with the PET Imaging manual instructions. Edits resulted in the removal of references.	Update.
Section 11	Removed references related to the updated paragraph in Section 7.3 as those citations are no longer relevant.	Update.

10.10. Version 10.0: 28 April 2023

Overall reason for Version 10.0: To reposition the assessment of HVA levels as a primary endpoint.

Protocol Section	Amendment/Update	Reason/ Rationale
Protocol	The version number and date were updated throughout. Editorial and administrative revisions (eg, typographical error, punctuation, tenses, abbreviations) were incorporated to provide clarity. The synopsis was updated to be consistent with changes in the protocol.	Update
Section 1.1.1	The current treatments for AADC deficiency were updated to reflect that eladocagene exuparvovec has approval in the European Union and United Kingdom.	Update
Section 1.2	The status of ongoing and completed studies was updated.	Update
Section 1.3	The rationale for using HVA level as an endpoint was added.	Update
Section 1.4	Evaluation of HVA levels was added as a purpose of this study.	Update
Section 2, Section 3.1, Section 7.2, Section 7.3, and Section 8	The objectives and endpoints were amended so that HVA level at Week 8 is a primary endpoint, and all previous exploratory endpoints are now secondary endpoints.	Update
Table 3	The window for the final visit (Week 96) was extended to 2 weeks following feedback on practicability.	Update
Section 7.5.5	Clarification was added that adverse events can be attributed to either the gene therapy, the cannula, or surgery.	Clarification

10.11. Version 11.0: 01 September 2023

Overall reason for Version 11.0: To extend the study duration to a total of 60 months (5 years).

Protocol Section	Amendment/Update	Reason/ Rationale
Protocol	The version number and date were updated throughout. Editorial and administrative revisions (eg, typographical error, punctuation, tenses, abbreviations) were incorporated to provide clarity. The objectives and endpoints were amended to reflect the change in the length of the study.The study length was revised to 5 years (60 months) and the word “optional” was removed from the description of the Long-Term Extension Study. The synopsis was updated to be consistent with changes in the protocol.	Update to reflect change in study length.
Section 1.2	Details pertaining to the ongoing Study 1602 were updated to reflect the most recent data.	Update
Section 2.2, 3.3 and 7.5.8	Added long-term efficacy through Month 60 to the description of secondary endpoints.	Update
Section 7.1, Table 3	Additional phone and in-person visits were added to reflect the extension of the total length of the study to 5 years (60 months) and capture the assessments that will be performed during those visits.	Update

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APPENDIX 1. PDMS-2 SCORE SHEET

PDMS-2

Examiner Record Booklet

Peabody Developmental Motor Scales

Second Edition

Section I. Identifying Information

Child's Name _____ Female ☐ Male ☐

First Administration	Year	Month	Day
Date Tested	____	____	____
Date of Birth	____	____	____
Chronological Age	____	____	____
Prematurity Adjustment		−____	−____
Corrected Age	____	____	____
Age in Months		____	

Examiner's Name _____

Examiner's Title _____

Subtest Results

	Raw Score		Raw Score
Reflexes	____	Object Manipulation	____
Stationary	____	Grasping	____
Locomotion	____	Visual-Motor Integration	____

Second Administration	Year	Month	Day
Date Tested	____	____	____
Date of Birth	____	____	____
Chronological Age	____	____	____
Prematurity Adjustment		−____	−____
Corrected Age	____	____	____
Age in Months		____	

Examiner's Name _____

Examiner's Title _____

Subtest Results

	Raw Score		Raw Score
Reflexes	____	Object Manipulation	____
Stationary	____	Grasping	____
Locomotion	____	Visual-Motor Integration	____

Third Administration	Year	Month	Day
Date Tested	____	____	____
Date of Birth	____	____	____
Chronological Age	____	____	____
Prematurity Adjustment		−____	−____
Corrected Age	____	____	____
Age in Months		____	

Examiner's Name _____

Examiner's Title _____

Subtest Results

	Raw Score		Raw Score
Reflexes	____	Object Manipulation	____
Stationary	____	Grasping	____
Locomotion	____	Visual-Motor Integration	____

Fourth Administration	Year	Month	Day
Date Tested	____	____	____
Date of Birth	____	____	____
Chronological Age	____	____	____
Prematurity Adjustment		−____	−____
Corrected Age	____	____	____
Age in Months		____	

Examiner's Name _____

Examiner's Title _____

Subtest Results

	Raw Score		Raw Score
Reflexes	____	Object Manipulation	____
Stationary	____	Grasping	____
Locomotion	____	Visual-Motor Integration	____

7 8 9 10 11 09 08 07 06 05

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Section II. Record of Item Performance

Item #	Age in Months	Item NAME, *Position*, and Description	Score Criteria	Administration 1	2	3	4
Gross Motor Scales							
Reflexes							
1 Start: 1–11 months	2	WALKING REFLEX With hands around trunk, hold child in standing position (facing away). Tilt child slightly forward. Brush top of child's feet against edge of table, then hold child so feet are resting on table.	2 Lifts 1 foot, then the other, in forward walking movement within 3 seconds 1 Lifts 1 foot within 3 seconds 0 Feet and legs remain still				
2	4	POSITIONING REFLEX: Asymmetrical Tonic Neck Reflex (Integrated) *(Lying on back, head toward examiner)* Turn child's face so left cheek is parallel to surface. Hold his or her head in that position for 3 seconds and observe child's reaction. Repeat procedure to right side.	2 Does not move arms and legs as a result of head being turned 1 Arms and legs respond as described below, but can move arms and legs out of position while head is turned 0 Reflex still present [When face is turned left, left arm and leg extend while right arm and right leg flex. When face is turned right, right arm and right leg extend while left arm and left leg flex. Reflex disappears by 6 months.]				
3	6	LANDAU REACTION Hold child suspended horizontally, stomach toward floor, side toward you with your hands under his or her chest and stomach.	2 Raises head above horizontal plane, extends trunk, and symmetrically raises hips and legs into full extension 1 Extends head above plane and extends trunk but hips and legs remain below horizontal 0 Head and hips remain below horizontal				
4	6	PROTECTING REACTION—Forward [Either kneel on floor or stand facing table so when child is tilted forward, he or she can reach surface.] Hold child in suspended horizontal position, stomach parallel to floor, buttocks toward you, then quickly tilt child's head toward the surface.	2 Extends arms, straightens elbows, and bears weight on open palms 1 Extends arms or puts hands on surface, elbows bent, but doesn't bear weight 0 Fails to extend arms or put hands on surface				
5	6	PROTECTING REACTION—Side *(Sitting, back toward you)* With hands at hips, support child in sitting position, then quickly tilt child 45 degrees to one side.	2 Breaks fall by extending arm and supporting self with open palm for 2 seconds 1 Breaks fall by falling on forearm 0 Falls on side				
6	6	PROTECTING REACTION—Forward *(Sitting, back toward you)* With hands at hips, support child in sitting position, then quickly tilt child 45 degrees forward.	2 Breaks fall by extending one or both arms and supporting self with one or both open palms for 2 seconds 1 Extends one or both arms and falls forward 0 Fails to extend arms				
7	9	RIGHTING REACTION—Forward *(Sitting, back toward you)* Place your hands on child's shoulders and pull him or her backward 20 degrees from vertical. (Be prepared to catch child if no reaction occurs.)	2 Extends arms and head forward to recover balance and returns to upright sitting position 1 Extends arms forward and to floor to recover balance and returns to upright sitting position 0 Fails to extend arms or head forward				
8	10	PROTECTING REACTION—Backward *(Sitting, facing you)* Place your hands on child's chest and push gently and rapidly backward at least 45 degrees. (Have someone prepared to catch child or stop fall if no reaction occurs.)	2 Stops fall by extending arm(s) backward and supporting weight on open palm(s) 1 Rotates trunk to one side and extends arm but continues to fall 0 Fails to extend arms				

Item #	Age in Months	Item NAME, *Position*, and Description	Score Criteria	Administration 1	2	3	4
Stationary							
1 Start: 1–2 months	0	ROTATING HEAD *(Lying on stomach, head turned to side with cheek resting on surface; examiner out of eyesight)* Shake **rattle** 3 times behind child's head. Repeat procedure with opposite cheek resting on surface.	2 Lifts and turns head so opposite cheek touches surface (both sides) 1 Lifts and turns head so opposite cheek touches surface (1 side only) 0 Head remains as positioned				
2	0	ALIGNING TRUNK *(Sitting, facing you)* Support child in sitting position by holding his or her wrists and arms. Observe position of child's back.	2 Holds back in rounded position for 3 seconds 1 Holds back in rounded position for 1–2 seconds 0 Arches back immediately				
3	1	ALIGNING HEAD—Front *(Sitting, head hanging forward, back to you)* With hands around trunk, support child in sitting position. Observe head alignment in relation to trunk.	2 Holds head so that a 45-degree angle (or greater) exists between chin and chest 1 Holds head up slightly from chest 0 Chin touches chest				
4	1	ALIGNING HEAD—Back *(Lying on back, pulled to sitting)* Grasp child's hands and wrists and gently pull him or her to a sitting position. Observe head alignment during movement cycle and head position at end of cycle.	2 Holds head so that a 45-degree angle (or greater) exists between back of head and back 1 Holds head up slightly from back 0 Head touches back				
5 Start: 3 months	2	ALIGNING HEAD *(Lying on back, pulled to sitting)* Grasp child's hands and wrists and gently pull to a sitting position. Observe head alignment during movement cycle and head position at end of cycle.	2 Holds head in midline through 75%–100% of movement cycle 1 Holds head in midline through 50%–74% of movement cycle 0 Holds head in midline for less than 50% of cycle				
6	2	EXTENDING HEAD *(Held in a suspended vertical position with head toward ceiling, feet toward floor)* Pick child up (facing you) with your hands around trunk. Observe head alignment.	2 Raises head at midline and holds it in alignment for 3 seconds 1 Raises head at midline and holds it in alignment for 1–2 seconds 0 Head remains extended backward or flexed forward				
7 Start: 4–5 months	2	ALIGNING HEAD *(Held at shoulder)* Hold child at your shoulder with one hand under buttocks and other on child's back. (Head is not supported.) Gently bounce child up and down 3 times.	2 Holds head in midline for 2–3 bounces 1 Holds head in midline for 1 bounce 0 Fails to hold head in midline on each bounce				
8	3	ALIGNING HEAD *(Held in suspended vertical position with head toward ceiling, feet toward floor)* Pick child up (facing you) with your hands around trunk. Slowly tilt child 45 degrees to left of midline. Without pausing, return to midline and tilt 45 degrees to right. Return to midline. Observe alignment of child's head throughout cycle. (Count 4 seconds per segment of movement cycle: left, midline, right, midline.)	2 Holds head in alignment for 75%–100% of movement cycle 1 Holds head in alignment for 50%–74% of movement cycle 0 Holds head in alignment for less than 50% of cycle				
9	3	STABILIZING TRUNK *(Sitting)* Support child in sitting position (side toward you) by holding his or her hips. Child's hands can be placed on surface for additional support.	2 Holds trunk off legs in a 30-degree angle for 5 seconds 1 Holds trunk off legs in less than a 30-degree angle for 5 seconds 0 Trunk remains in contact with legs				

Item #	Age in Months	Item NAME, *Position*, and Description	Score Criteria	Administration 1	2	3	4
10 Start: 6 months	4	ALIGNING HEAD *(Sitting, supported with pillows around hips)* Dangle **toy on a string** 12 in. in front of child. Slowly move toy in 180-degree arc, from in front of child to his or her left side, back to front, and then to right side. (Count 4 seconds per segment of movement cycle: left, front, right, front.)	2 Holds head aligned for 8 seconds while rotating head to follow toy 1 Holds head aligned for 4–7 seconds while rotating head to follow toy 0 Holds head aligned for less than 4 seconds				
11	5	SITTING Place child in sitting position, hands on surface beside knees. When balance is secure, release child.	2 Maintains balance for 8 seconds 1 Maintains balance for 3–7 seconds 0 Maintains balance for less than 3 seconds				
12 Start: 7–9 months	6	SITTING/REACHING *(Sitting, pillows supporting hips)* Attract child's attention to **toy on a string** suspended at midline 12 in. in front of child's chest.	2 Maintains balance for 8 seconds while extending arms and hands to grasp toy 1 Maintains balance for 5–7 seconds while extending arms and hands to grasp toy 0 Maintains balance for less than 5 seconds				
13	6	PULLING TO SIT *(Lying on back, feet toward you)* Hold index fingers out, touching child's hands, if necessary, to get child to grasp them. Once fingers are grasped, say, "Get up." Pull your hands back so child's arms become straight.	2 Pulls up to sitting position 1 Pulls up 45–90 degrees from the surface 0 Pulls up less than 45 degrees or remains lying on surface				
14 Start: 10–11 months	6	SITTING Place child in sitting position and release your support.	2 Sits unsupported for 60 seconds 1 Sits unsupported for 30–59 seconds 0 Sits for less than 30 seconds				
15	7	SITTING WITH TOY Place child in sitting position and release your support. Place **toy** 12 in. in front of child. Say, "Get the toy."	2 Retrieves toy, returns to upright sitting, and maintains balance for 30 seconds 1 Retrieves toy, returns to upright sitting, and maintains balance for 15–29 seconds 0 Fails to retrieve toy, return to upright sitting, or maintain balance for 15 seconds				
16 Start: 12–15 months	9	SITTING Place child in sitting position and release your support. Give **toy** to child and say, "Play with the toy."	2 Maintains balance for 60 seconds while manipulating toy 1 Maintains balance for 30–59 seconds while manipulating toy 0 Maintains balance for less than 30 seconds				
17	10	RAISING TO SIT *(Lying on back)* Place child on back on floor. Attract child's attention to **toy** and then place it on chair where child can see it. Say, "Get the toy."	2 Pulls up to sitting position, using chair for support 1 Grasps chair and rotates body in effort to raise up 0 Remains lying on floor				
18	10	SITTING UP *(Lying on stomach)* Place child on stomach on floor. Attract child's attention to **toy**; then hold toy out of child's reach, about 2 ft. above floor. Say, "Get the toy."	2 Raises to sitting position 1 Attempts to maneuver into sitting position 0 Remains lying on floor				
19 Start: 16–26 months	13	KNEELING Place child in a kneeling position, buttocks not resting on heels. Keeping toy at child's eye level and about 2 ft. away, move it in arc to one side of child. Say, "Watch the **toy**." Return toy to starting position and then move it in arc to other side. (Take about 4 seconds for each segment of movement cycle: front to left, left to front, front to right, right to front.)	2 Maintains balance for 5 seconds while rotating head 1 Maintains balance for 2–4 seconds 0 Maintains balance for less than 2 seconds				

Item #	Age in Months	Item NAME, *Position*, and Description	Score Criteria	Administration 1	2	3	4
20 Start: 27–48 months	31–32	STANDING ON 1 FOOT Stand on 1 foot, hands on hips with free leg bent back at knee. Say, "Put your hands on your hips and stand on 1 foot like I did."	2 Stands on 1 foot with hands on hips for 3 seconds 1 Stands on 1 foot with hands on hips for 1–2 seconds 0 Requires help to stand on 1 foot				
21	41–42	STANDING ON 1 FOOT Stand on 1 foot, hands on hips with free leg bent back at knee. Say, "Put your hands on your hips and stand on 1 foot like I did."	2 Stands on 1 foot with hands on hips for 5 seconds 1 Stands on 1 foot with hands on hips for 2–4 seconds 0 Stands on 1 foot for less than 2 seconds				
22 Start: 49–56 months	43–44	STANDING ON TIPTOES Stand on tiptoes with hands held overhead for 3 seconds. Say, "Hold your hands over your head and stand on your tiptoes like I did."	2 Stands on tiptoes with arms held overhead and without moving feet for 3 seconds 1 Stands on tiptoes with arms held overhead and without moving feet for 1–2 seconds 0 Moves feet or heels remain on floor				
23	45–46	STANDING ON 1 FOOT Stand on 1 foot, hands on hips with free leg bent back at knee for 5 seconds. Say, "Put your hands on your hips and stand on 1 foot like I did."	2 Stands on 1 foot with hands on hips and without swaying more than 20 degrees for 5 seconds 1 Stands on 1 foot with hands on hips and without swaying more than 20 degrees for 2–4 seconds 0 Stands on 1 foot for less than 2 seconds or sways more than 20 degrees				
24 Start: 57–71 months	51–52	STANDING ON TIPTOES Stand on tiptoes with hands held overhead for 8 seconds. Say, "Hold your hands over your head and stand on your tiptoes like I did for as long as you can."	2 Stands on tiptoes with arms held overhead, without moving feet, and without swaying more than 20 degrees for 8 seconds 1 Stands on tiptoes with arms held overhead, without moving feet, and without swaying more than 20 degrees for 5–7 seconds 0 Stands on tiptoes for less than 5 seconds or sways more than 20 degrees				
25	53–54	STANDING ON 1 FOOT Stand on 1 foot with hands on hips for 10 seconds, then on other foot for 10 seconds. Say, "Put your hands on your hips and stand on each foot like I did." Count seconds out loud to encourage child to balance longer.	2 Stands on 1 foot, then on other foot, with hands on hips and without swaying more than 20 degrees for 6 seconds on each foot 1 Stands on one foot, then on other foot, with hands on hips and without swaying more than 20 degrees for 1–5 seconds on each foot 0 Stands on only 1 foot (does not change feet) or sways more than 20 degrees				
26	57–58	IMITATING MOVEMENTS *(Standing)* Stand 3 feet from child. Say, "I am going to move my arms and I want you to copy my movements." Do practice move (one not on test) to see if child understands. Do not use verbal cues. Present 6 positions one at a time at 1-second intervals.	2 Imitates 4 positions accurately 1 Imitates 1–3 positions accurately 0 Fails to imitate any position accurately				
27	59–60	STANDING ON 1 FOOT Stand on 1 foot with hands on hips for 10 seconds, then on the other foot for 10 seconds. Say, "Put your hands on your hips and stand on 1 foot and then the other like I did." Count seconds out loud to encourage child to balance longer.	2 Stands on each foot with hands on hips and without swaying more than 20 degrees for 10 seconds 1 Stands on each foot with hands on hips and without swaying more than 20 degrees for 5–9 seconds 0 Stands on each foot for less than 5 seconds, sways more than 20 degrees, or stands on only 1 foot				

Item #	Age in Months	Item NAME, *Position*, and Description	Score Criteria	Administration 1	2	3	4
28	59–60	SIT-UPS *(Lying down on mat)* Demonstrate sit-ups on mat. Place child in starting position on mat. Hold child's feet and say, "Do as many sit-ups as you can." Stop child after 30 seconds.	2 Completes 3 sit-ups in 30 seconds 1 Completes 1–2 sit-ups in 30 seconds 0 Fails to complete any sit-ups				
29	68–72	SIT-UPS *(Lying down on mat)* Demonstrate sit-ups on mat. Place child in starting position on mat. Hold child's feet and say, "Do as many sit-ups as you can." Stop child after 30 seconds.	2 Completes 5 sit-ups in 30 seconds 1 Completes 3–4 sit-ups in 30 seconds 0 Completes less than 3 sit-ups				
30	72	PUSH-UPS *(Lying face down on mat)* Demonstrate 3 push-ups. Say, "Do as many push-ups as you can." Stop child after 20 seconds.	2 Completes 8 push-ups in 20 seconds 1 Completes 4–7 push-ups in 20 seconds 0 Completes less than 4 push-ups				
		Locomotion					
1 Start: 1–2 months	0	THRUSTING LEGS *(Lying on back)* Stimulate leg thrusts by holding child's feet and pushing them toward his or her body so knees are flexed, legs bent, and heels almost touching buttocks. Then pull child's feet out until legs are fully extended. Repeat motions. Let go of child's feet. Observe for more than 1 minute.	2 Bends and straightens legs (alternately or together) 2 times 1 Bends and straightens legs (alternately or together) 1 time or moves only 1 leg 0 Does not move legs				
2	0	TURNING FROM SIDE TO BACK *(Lying on side, legs bent to maintain balance, examiner in back of child)* Shake **rattle** 3 times behind child's back. Repeat procedure with child lying on opposite side.	2 Rolls onto back (both sides) 1 Rolls onto back (1 side only) 0 Remains on side				
3	0	THRUSTING ARMS *(Lying on back)* Stimulate arms by bringing child's hands together at midchest with elbows bent. Then stretch arms out to sides until elbows are straight and hands touch surface. Repeat. Let go of child's hands. Observe for 1 minute.	2 Bends and straightens arms (alternately or together) 2 times 1 Bends and straightens arms (alternately or together) 1 time or moves only 1 arm 0 Does not move arms				
4	2	BEARING WEIGHT *(Standing)* Hold child in a standing position facing you with his or her feet resting on table or counter top. Observe leg position and whether child can bear weight for 3 seconds.	2 Bears weight with knees flexed and feet flat for 3 seconds 1 Bears weight with knees flexed and toes touching surface for 3 seconds or with knees flexed and feet flat for 1–2 seconds 0 Fails to bear weight or legs remain straight with only toes touching surface				
5 Start: 3–4 months	2	EXTENDING TRUNK *(Lying on stomach, head turned to side, forearms resting on surface)* Attract child's attention by shaking **rattle** 1 in. above surface. Continue to shake rattle and move it 6 in. above child's head.	2 Elevates head and upper trunk 45 degrees, bearing weight on forearms or hands for 3 seconds 1 Elevates head and upper trunk 45 degrees, bearing weight on forearms or hands for 1–2 seconds 0 Elevates head less than 45 degrees				
6	3	SYMMETRICAL POSTURE *(Lying on back; feet toward you)* Shake **rattle** 18 in. from child's nose and then move it to within 12 in.	2 Brings both hands together at midline within 5 seconds (hands come up together) while maintaining midline head and body posture 1 Brings 1 hand to midline and moves the other out of midline while maintaining midline head and body posture 0 Hands remain out of midline position				

Item #	Age in Months	Item NAME, *Position*, and Description	Score Criteria	Administration 1	2	3	4
7 Start: 5 months	4	PROPPING ON FOREARMS *(Lying on stomach, chin and forearms resting on surface)* Attract child's attention to **toy on a string** and then suspend it 12 in. above child's face.	2 Elevates head and upper trunk 45 degrees and bears weight on forearms for 5 seconds 1 Elevates head and upper trunk 45 degrees and bears weight on forearms for 3–4 seconds 0 Elevates head and upper trunk, bearing weight for less than 3 seconds, or fails to elevate trunk				
8	4	ROLLING *(Lying on back, feet toward you)* Shake **rattle** at midline 12 in. above child's face. Slowly move rattle in arc toward surface. Repeat procedure to other side.	2 Rolls to side with opposite arm crossing midline (both sides) 1 Rolls to side with opposite arm crossing midline (one side only) 0 Remains on back				
9 Start: 6 months	4	EXTENDING ARMS AND LEGS *(Lying on stomach, head toward you)* Attract child's attention to **toy on a string** that you dangle at midline 12 in. from child's head. Observe child's arms and legs for 5 seconds.	2 Extends arms and legs (alternately or together) off surface for 3 seconds 1 Extends arms and legs (alternately or together) off surface for 1-2 seconds, or moves only arms or legs for 3 seconds 0 Arms and legs remain inactive				
10	5	FLEXING LEGS *(Lying on back, bare feet)* If child has socks on, remove them and then gently bend both legs toward child's face, wiggle and then release them.	2 Brings feet to mouth for play or grabs feet with hands (both feet must come up, alternately or together) 1 Raises feet 90 degrees or less or brings 1 foot to mouth 0 Legs remain on surface				
11	5	EXTENDING ARMS AND LEGS *(Lying on back, head in midline)* Attract child's attention to **toy on a string** that you dangle at midline 12 in. from child's head. Observe child's arms and legs for 5 seconds.	2 Raises arms and legs (alternately or together) in smooth, fluid movements within 5 seconds after toy is presented 1 Raises arms and legs (alternately or together) within 6–7 seconds after toy is presented 0 Arms and legs remain inactive				
12	6	EXTENDING ARM *(Lying on stomach, chin and forearms resting on surface)* Attract child's attention to **toy on a string** just out of reach. Say, "Get the toy."	2 Raises upper trunk, shifts weight to side, lifts free arm, and reaches toward toy 1 Raises upper trunk, shifts weight to side, and lifts free arm without reaching toward toy 0 Both arms remain in contact with surface				
13 Start: 7 months	6	FLEXING BODY *(Lying on back, bare feet)* Gently bend both legs toward head 3 times. Do not place feet in child's hands, but encourage child to grasp them by saying, "Get your feet."	2 Grasps both feet and holds them for 3 seconds 1 Grasps both feet and holds them for 1–2 seconds or grasps 1 foot and holds it for 3 seconds 0 Legs remain on surface				
14	6	PUSHING UP *(Lying on stomach, head turned to side, forearms resting on surface)* Attract child's attention to **rattle.** Shake rattle 12 in. in front of child's forehead and 6 in. above child's head.	2 Elevates head and stomach by pushing up with arms, bearing weight on palms for 5 seconds 1 Elevates head and stomach by pushing up with arms, bearing weight on palms for 3–4 seconds 0 Bears weight for less than 3 seconds				
15	6	EXTENDING ARM *(Lying on back)* Shake **toy on a string** and then hold it 12 in. to right of child's head and 12 in. above surface. Repeat procedure to opposite side.	2 Shifts weight to side and supports self with arm for 3 seconds while extending opposite arm to reach for toy (both sides) 1 Shifts weight to side and supports self with arm for 1–2 seconds while extending opposite arm to reach for toy (1 or both sides) 0 Remains on back				

Item #	Age in Months	Item NAME, *Position*, and Description	Score Criteria	Administration 1	2	3	4
16	7	ROLLING *(Lying on back)* Shake **rattle** at midline 12 in. above child. Lower rattle to surface on child's left, out of child's reach. Repeat procedure on opposite side.	2 Rolls from back to stomach (both sides) 1 Rolls from back to stomach (1 side only) 0 Remains on back				
17 Start: 8 months	7	ROLLING *(Lying on back)* Attract child's attention to **toy** by shaking it to side of child. Repeat procedure on opposite side.	2 Rolls from back to stomach, leading with hips and thighs, followed by stomach and then shoulders (both sides) 1 Rolls from back to stomach (1 side only) 0 Remains on back				
18 Start: 9 months	8	MOVING FORWARD *(Lying on stomach)* Place **toy** 5 ft. in front of child. Say, "Get the toy."	2 Moves forward 3 ft. using arms 1 Moves forward at least 2 ft. but less than 3 ft. using arms 0 Moves less than 2 ft.				
19 Start: 10 months	9	RAISING SHOULDERS AND BUTTOCKS *(Lying on stomach)* Sit 3 ft. in front of child. Hold your hands out to child and say, "Come here."	2 Raises and bears weight on hands and knees for 5 seconds and rocks back and forth for 2 cycles 1 Raises and bears weight on hands and knees for 1–5 seconds 0 Remains on stomach				
20	9	CREEPING *(Hands and knees)* Place **toy** on floor 6 ft. in front of child. Say, "Get the toy." Move toy back as child approaches.	2 Creeps forward on hands and knees, using a cross-lateral pattern (opposite arms and legs moving together) for 5 ft. 1 Creeps forward on hands and knees using cross-lateral pattern for 4 ft. or creeps without using cross-lateral pattern for 5 ft. 0 Remains stationary or moves on stomach				
21	9	SCOOTING *(Sitting)* Sit beside child on floor. Say, "Watch me." Demonstrate scooting by using your hands to propel your body forward on your buttocks to retrieve toy. Place **toy** 5 ft. in front of child. Say, "Scoot like I did and get the toy."	2 Maintains sitting posture and uses hands and legs to scoot forward 3 ft. 1 Maintains sitting posture and scoots forward 1–2 ft. 0 Moves less than 1 ft. forward				
22 Start: 11 months	9	PIVOTING *(Sitting)* Place child in sitting position on floor. Attract child's attention to **toy**, then place it 2 ft. from child's right side. Say, "Turn and get the toy." Repeat procedure on opposite side.	2 Turns on buttocks using legs or arms to pivot body 90 degrees (both sides) 1 Turns on buttocks using legs or arms to pivot body 90 degrees (1 side only) 0 Pivots less than 90 degrees				
23	9	STANDING *(Sitting next to stable object, such as chair or table)* Attract child's attention to **toy**, then place it on edge of stable object, out of child's reach. Say, "Get the toy."	2 Raises to standing position using stable object for support 1 Attempts to raise to standing, but returns to sitting 0 Makes no attempt to stand				
24	10	CREEPING *(Sitting on floor to one side of you)* Sit with legs straight and knees touching. Attract child's attention to **toy**, then place toy on the other side of your legs so child will have to climb across your legs to retrieve it. Say, "Get the toy."	2 Creeps completely over your legs 1 Creeps onto your legs 0 Remains stationary or creeps up to your legs				
25	10	BOUNCING *(Standing)* Have child hold your index fingers. Stimulate bouncing by moving your hands up and down 2 times.	2 Bounces 3 times by flexing knees 1 Bounces 1–2 times by flexing knees 0 Stiffens legs or sits down				
26 Start: 12 months	10	CRUISING *(Standing next to low table)* Place child in standing position at end of table. Place **toy** on opposite end of table. Say, "Get the toy."	2 Takes 4 steps sideways (holding on to table) 1 Takes 1–3 steps sideways (holding on to table) 0 Remains stationary				

Item #	Age in Months	Item NAME, *Position*, and Description	Score Criteria	Administration 1	2	3	4
27	10	LOWERING Place child in standing position with side next to stable object (chair or low table) for support. Place **toy** on floor in front of child. Say, "Sit down and play with the toy."	2 Lowers to sitting position without falling 1 Lowers self, but falls in process 0 Remains standing				
28	10	STEPPING With child facing you, support child in standing position with your hands around trunk. Say, "Let's walk."	2 Takes 4 alternating steps in place or forward 1 Takes 2–3 alternating steps in place or forward 0 Fails to take alternating steps				
29 Start: 13 months	11	PIVOTING Place child in sitting position straddling one line of **taped 3 × 3 ft. cross.** Attract child's attention to **toy**, then place it on line 2 ft. behind child. Say, "Turn and get the toy."	2 Pivots 180 degrees (straddles line in opposite direction), while remaining seated 1 Pivots 90–179 degrees (body midline fails to straddle line), while remaining seated 0 Pivots less than 90 degrees				
30	11	STANDING Place child in standing position next to stable object (chair or low table). Stand 4 ft. in front of child with your arms outstretched. Say, "Come here."	2 Frees hands and body from support and maintains balance in standing position for 5 seconds 1 Frees hands and body from support and maintains balance in standing position for 2–4 seconds 0 Fails to release support				
31	11	STANDING Place child in standing position away from anything that can be used for support. Release your support of child. (Be ready to catch child if necessary.)	2 Maintains balance for 3 seconds before showing instability or dropping to floor 1 Maintains balance for 1–2 seconds before showing instability or dropping to floor 0 Immediately shows signs of instability or drops to floor				
32	11	STEPPING From in front, support child in standing position by holding 1 hand. Say, "Let's walk."	2 Takes 4 alternating steps in place or forward 1 Takes 2–3 alternating steps in place or forward 0 Fails to take alternating steps				
33 Start: 14 months	12	STANDING UP *(Sitting cross-legged on floor)* Demonstrate standing up from sitting position. Place palms of hands on floor beside hips. Push down with hands, straighten arms, and shift weight to feet. Stand up without turning body more than 20 degrees to either side. Say, "Get up like I did."	2 Stands without turning body more than 20 degrees 1 Stands but turns body 21–90 degrees 0 Turns body more than 90 degrees or fails to stand				
34	12	WALKING *(Standing)* From the side, support child by holding 1 hand. Say, "Let's walk."	2 Uses alternating steps to walk 8 ft. 1 Uses alternating steps to walk 4–7 ft. 0 Walks less than 4 ft.				
35	12	WALKING *(Standing)* Hold **toy** 2 ft. in front of child. Say, "Come get the toy." Move back as needed to keep toy just out of reach.	2 Walks unaided for 5 steps 1 Walks unaided for 1–4 steps 0 Remains stationary or sits down				
36	13	STANDING AND MOVING BALANCE *(Standing)* Place **toy** on floor 2 ft. in front of child. Say, "Get the toy and bring it to me."	2 Picks up toy, returns to standing, and takes 3 steps without losing balance 1 Picks up toy, returns to standing, and takes 1–2 steps before losing balance 0 Remains stationary or loses balance when picking up toy				

Item #	Age in Months	Item NAME, *Position*, and Description	Score Criteria	Administration 1	2	3
37 Start: 15–16 months	14	CREEPING UP STAIRS *(Sitting on floor, facing stairs)* Place **toy** on 3rd step. Say, "Get the toy." Move toy up as child gets closer. (Be prepared to catch child if necessary.)	2 Creeps up 2 steps on hands and knees 1 Creeps up 1 step on hands and knees 0 Remains on 1st step			
38	14	WALKING Stand 10 ft. in front of child and hold your arms out. Say, "Come to me." **[Record the time it takes to walk 10 ft. for use in Item 41.]** _____ Time to walk 10 ft.	2 Walks 10 ft. with narrow base of support, heel–toe gait, using a reciprocal pattern for at least half the distance 1 Walks 4–9 ft. with narrow base of support, heel–toe gait, using a reciprocal pattern for at least half the distance 0 Walks with wide base of support (feet positioned at shoulder width) and/or arms held out to sides, parallel to surface			
39 Start: 17–18 months	15–16	CREEPING DOWN STAIRS *(On stairs, knees on 4th step, hands on 5th step)* Stand 2 or 3 steps below child. Say, "Come to me." Move backward as necessary.	2 Creeps backward down 3 steps without support (from adult or rail) 1 Creeps backward down 1–2 steps without support (from adult or rail) 0 Remains on 4th step			
40	15–16	WALKING UP STAIRS *(Standing, facing flight of stairs, close to railing or wall)* Place **toy** on 6th step. Get behind child and say, "Walk up the steps and get the toy."	2 Walks up 4 steps with support from wall or rail (may place 1 or both feet on each step) 1 Walks up 1–3 steps with support from wall or rail 0 Remains stationary or drops to hands and knees to ascend steps			
41 Start: 19–20 months	17–18	WALKING FAST Run away from child and say, "Catch me!" _____ Record time to walk 10 ft. _____ Time recorded in Item 38	2 Walks 10 ft. in ½ the time recorded in Item 38 1 Walks 10 ft. in more than ½ but less than ¾ of the time recorded in Item 38 0 Walks 10 ft. in ¾ or more of the time recorded in Item 38			
42	17–18	WALKING BACKWARD Walk backward while pulling **pull toy**. Give cord to child and say, "You pull it like I did."	2 Walks backward 5 steps (may or may not pull toy while walking) 1 Walks backward 2–4 steps 0 Takes less than 2 steps backward			
43 Start: 21–22 months	17–18	WALKING DOWN STAIRS *(Standing on 4th step, next to wall or railing, facing down)* Stand beside child and offer him or her your finger. Say, "Let's walk down the steps."	2 Walks down 4 steps with support only from examiner's finger (may place 1 or both feet on each step) 1 Walks down 1–3 steps with support only from examiner's finger 0 Remains stationary or lowers to sitting to descend steps			
44 Start: 23–24 months	17–18	WALKING BACKWARD Demonstrate walking backward using a normal stride (heels not touching toes). Say, "Walk backward like I did."	2 Walks backward 5 steps 1 Walks backward 2–4 steps 0 Walks backward less than 2 steps			
45	19–20	RUNNING Stand 12 ft. in front of child. Say, "Run to me as fast as you can."	2 Runs forward 10 ft. 1 Runs forward 5–9 ft. 0 Walks or runs less than 5 ft.			
46	19–20	STANDING **Taped line (2 in. × 2 ft.)** Stand on line with 1 foot in front of other, toe of back foot touching heel of front foot. Say, "Stand on the line like I did."	2 Stands on line with 1 foot in front of other for 2 seconds; toe of back foot is within 3 in. of front foot 1 Places 1 foot on line and attempts to place other foot on line 0 Makes no attempt to place 2nd foot on line			

Item #	Age in Months	Item NAME, *Position*, and Description	Score Criteria	Administration 1	2	3	4
47 Start: 25–26 months	21–22	WALKING SIDEWAYS Face child and say, "Watch me." Step sideways, leading with same foot, for 10 ft. Say, "Walk like I did."	2 Walks sideways for 10 ft., leading with same foot 1 Walks sideways 4–9 ft., leading with same foot for half the steps 0 Remains stationary or walks in a manner other than sideways				
48	21–22	WALKING LINE **Taped line (4 in. × 8 ft.)** Walk on the line with 1 foot on line and other foot beside it. Say, "Walk on the line like I did."	2 Walks with 1 foot on line for 6 ft. 1 Walks with 1 foot on line for 4–5 ft. 0 Walks for less than 4 ft. on line				
49	23–24	JUMPING FORWARD **Taped line on floor (2 in. × 2 ft.)** Using 2-footed takeoff and landing, jump forward 12 in. from starting line. Say, "Jump like I did." Measure distance from line to point where nearest heel touches floor.	2 Jumps forward 4 in., maintaining balance 1 Jumps less than 4 in. forward, maintaining balance 0 Steps forward or falls				
50	23–24	JUMPING UP Demonstrate jumping up with your feet together, knees flexed, and body propelled upward. Say, "Jump like I did."	2 Jumps up 2 in. with feet together 1 Jumps up with feet barely leaving floor, or jumps up 2 in. with 1 foot leading the other 0 Keeps toes in contact with floor				
51 Start: 27–30 months	23–24	JUMPING DOWN *(Standing on step 7 in. high)* Stand in front of child and say, "Jump down."	2 Jumps down without assistance; 1 foot may lead 1 Steps down without assistance 0 Needs assistance to get down				
52	23–24	WALKING UP STAIRS *(Standing, facing flight of stairs, at middle of step width)* Place **toy** on 6th step. Say, "Walk up the steps without holding on."	2 Walks up 4 steps without support from wall or rail (may place 1 or both feet on each step) 1 Walks up 4 steps using rail or wall for support 0 Remains stationary or drops to hands and knees to ascend stairs				
53	25–26	WALKING DOWN STAIRS *(Standing on 4th step, facing down stairs, next to wall or railing)* Stand 2 steps below child. Say, "Walk down to me." Move down as child begins to descend.	2 Walks down 4 steps without support by placing 1 or both feet on each step 1 Walks down 1–3 steps without support 0 Remains stationary or uses wall or rail for additional support				
54	25–26	WALKING BACKWARD Demonstrate walking backward 10 ft. using a normal backward stride (without touching heels to toes). Say, "Walk backward like I did."	2 Walks backward 10 ft. without heels touching toes 1 Walks backward 1–9 ft. 0 Walks backward less than 1 ft.				
55	25–26	JUMPING UP *(Standing next to wall)* **Mark on wall at standing reach and line 2 in. higher** Demonstrate jumping up and touching wall as high as you can. Point to line and say, "Jump up and touch as high as you can."	2 Jumps up and touches line or above 1 Jumps up and touches between mark and line 0 Keeps toes in contact with floor or fingers touch below mark				
56	27–28	WALKING LINE **Taped line (4 in. × 8 ft.)** Using a normal stride (heels not touching toes), walk forward 3 steps on line. Say, "Keep your hands on your hips and walk on the line like I did."	2 Takes 3 steps forward on line with hands on hips and without heels touching toes 1 Takes 1–2 steps forward on line with hands on hips and without heels touching toes 0 Walks with one foot off the line				

Item #	Age in Months	Item NAME, *Position*, and Description	Score Criteria	Administration 1	2	3	4
57 Start: 31–34 months	27–28	WALKING UP STAIRS *(Standing at foot of stairs)* Get behind child and say, "Walk up the steps."	2 Walks up 4 steps, placing 1 foot on each step, using wall or rail for support 1 Walks up 1–3 steps, placing 1 foot on each step, using wall or rail for support 0 Remains stationary or places both feet on each step and uses support				
58	29–30	JUMPING DOWN *(Standing on stable object 16–21 in. high)* Say, "Jump down."	2 Jumps down without assistance, 1 foot may lead 1 Steps down without assistance 0 Needs assistance to get down				
59	29–30	WALKING ON TIPTOES Walk on tiptoes with your hands on hips for 5 steps. Say, "Keep your hands on your hips and walk on your tiptoes like I did."	2 Walks on tiptoes for 5 steps with hands on hips and without heels touching floor 1 Walks on tiptoes for 1–4 steps with hands on hips and without heels touching floor 0 Walks with heels touching floor				
60 Start: 35–38 months	29–30	RUNNING SPEED With **taped lines (2 in. × 2 ft.) 30 ft. apart**, place child with toes behind starting line. Stand 1 yd. behind finish line and say, "Run to me as fast as you can." Time from when child starts running to when he or she crosses finish line.	2 Runs 30 ft. in 6 seconds or less 1 Runs 30 ft. in 7–9 seconds 0 Walks or runs 30 ft. in more than 9 seconds				
61	31–32	JUMPING FORWARD *(Standing with toes on line)* **Taped line (2 in. × 2 ft.)** Demonstrate jumping forward using 2-footed takeoff and landing. Say, "Jump like I did."	2 Jumps forward 24 in. using 2-footed takeoff and landing 1 Jumps forward 12–23 in. using 2-footed takeoff and landing 0 Jumps forward less than 12 in., steps forward, or falls				
62	31–32	JUMPING DOWN *(Standing on stable object 18–24 in. high)* Say, "Jump down with both feet together."	2 Jumps down without assistance using 2-footed takeoff and landing 1 Jumps down, taking off with 1 foot and landing on both feet without assistance, or takes off with 2 feet and falls on landing 0 Needs assistance to get down				
63	33–34	JUMPING HURDLES **String (or rope) tied between 2 chair legs, 2 in. off floor and 3 ft. apart** (Tie loosely to prevent tripping.) Stand 6 in. away from and facing string. Using 2-footed takeoff and landing, jump over string. Say, "Jump over the string like I did."	2 Jumps over string without tripping using 2-footed takeoff and landing 1 Jumps over string without tripping using 1-footed takeoff and landing 0 Steps over, or jumps but remains on same side				
64 Start: 39–42 months	33–34	WALKING ON TIPTOES **Taped line (4 in. × 8 ft.)** Walk on tiptoes, hands on hips, for entire length of line. Say, "Keep your hands on your hips and walk on your tiptoes like I did."	2 Walks on tiptoes for entire length of line with hands on hips and without heels touching floor 1 Walks on tiptoes for 1–7 ft. with hands on hips and without heels touching floor 0 Walks on tiptoes for less than 1 ft. on line				
65 Start: 43–45 months	35–36	WALKING UP STAIRS *(Standing centered at foot of stairs)* Place a **toy** on the 6th step. Stand behind child and say, "Walk up the steps and get the toy."	2 Walks up 4 steps without support, placing 1 foot on each step 1 Walks up 1–3 steps with support from wall or rail and placing 1 foot on each step, or walks up 4 steps without support but placing both feet on each step 0 Remains stationary or places both feet on each step and uses support				

Item #	Age in Months	Item NAME, *Position*, and Description	Score Criteria	Administration 1	2	3	4
66	37–38	RUNNING SPEED **Taped lines (2 in. × 2 ft.) 45 ft. apart** Place the child within 6 in. behind a taped line on the floor and then stand 3 ft. behind finish line. Say, "Run to me as fast as you can without stopping."	2 Runs 45 ft. in 6 seconds or less 1 Runs 45 ft. in 7–9 seconds 0 Walks or runs 45 ft. in more than 9 seconds				
67	39–40	JUMPING FORWARD **Taped line (2 in. × 2 ft.)** Demonstrate jumping forward using a 2-footed takeoff and landing. Say, "Jump like I did."	2 Jumps forward 26 in. using 2-footed takeoff and landing 1 Jumps forward 12–25 in. using 2-footed takeoff and landing 0 Jumps forward less than 12 in. or falls				
68 Start: 46–50 months	41–42	WALKING LINE **Taped line (4 in. × 8 ft.)** Using a normal stride (heels not touching toes), walk forward on line. Say, "Keep your hands on your hips and walk on the line like I did. Try not to step off the line."	2 Walks forward 4 ft. without stepping off line, with hands on hips and without heels touching toes 1 Walks forward 4 ft. on line, stepping off 1 time, with hands on hips and without heels touching toes 0 Steps off line more than once				
69	41–42	RUNNING FORM Say, "When I say go, run fast and keep running until I say stop." Stop child after 10 seconds.	2 Runs with arms moving back and forth across body and at or below waist, balls of feet used to push forward, toes pointed forward, a high knee and heel lift, and trunk leaning forward 1 Runs with arms held out to side, or feet remain flat during the run 0 Walks at any time during 10-second period				
70	41–42	WALKING LINE FORWARD **Taped line (4 in. × 8 ft.)** Using a normal stride (heels not touching toes) and with hands on hips, walk forward on line. Say, "Keep your hands on your hips and walk on the line like I did. Try not to step off the line."	2 Walks forward 8 ft. on line without stepping off, with hands on hips, without heels touching toes, and without swaying more than 20 degrees 1 Walks forward 8 ft. on line and steps off 1 time, with hands on hips, without heels touching toes, and without swaying more than 20 degrees 0 Steps off line more than once or sways more than 20 degrees				
71	43–44	WALKING DOWN STAIRS *(Standing on 4th step, facing down stairs)* Stand 2 or more steps below child and say, "Walk down the steps without holding on." Move down as child descends.	2 Walks down 4 steps, placing 1 foot on each step without support 1 Walks down 4 steps, placing both feet on 1 or 2 steps without support 0 Remains stationary or places both feet on each step for 3 or more steps				
72 Start: 51–54 months	43–44	JUMPING FORWARD ON 1 FOOT **Taped line (2 in. × 2 ft.)** Jump forward on 1 foot without letting other foot touch floor. Say, "Jump forward like I did." Measure from line to point where back of heel touches floor.	2 Jumps forward 6 in. on 1 foot without other foot touching floor 1 Jumps forward 2–5 in. on 1 foot without other foot touching floor 0 Jumps less than 2 in. or 2nd foot touches floor				
73	45–46	JUMPING UP *(Standing next to wall)* **Mark on wall at standing reach and line (2 in. × 1 ft.) 3 in. higher** Demonstrate jumping up and touching wall as high as you can. Point to line and say, "Jump and touch as high as you can."	2 Jumps up and touches line or above 1 Jumps up and touches between mark and line 0 Toes remain in contact with floor or fingers touch mark or below				

Item #	Age in Months	Item NAME, *Position*, and Description	Score Criteria	Administration 1	2	3	4
74	45–46	RUNNING BALANCE/COORDINATION Demonstrate running and stopping on command. Say, "When I say go, run until I say stop. Then stop as quickly as you can. Stay still until I say go. Then run until I say stop." Stop child after 3 cycles.	2 Runs and stops within 2 steps without falling 1 Runs and stops in 3 or more steps without falling 0 Fails to run or takes more than 3 steps to stop				
75 Start: 55–58 months	45–46	WALKING LINE BACKWARD **Taped line (4 in. × 8 ft.)** Using normal stride (heels not touching toes) and with hands on hips, walk backward on line. Say, "Put your hands on your hips and walk backward like I did."	2 Walks backward 4 ft. without stepping off line more than once, with hands on hips, and without heels touching toes 1 Walks backward 4 ft. on line and steps off 2–5 times with hands on hips and without heels touching toes 0 Steps off line more than 5 times				
76	47–48	JUMPING FORWARD **Taped line (2 in. × 2 ft.)** Demonstrate jumping forward using a 2-footed takeoff and landing. Say, "Jump like I did." Measure from line to point where back of nearest heel touches floor.	2 Jumps forward 30 in. using 2-footed takeoff and landing 1 Jumps forward 20–29 in. using 2-footed takeoff and landing 0 Jumps forward less than 20 in. or falls				
77	47–48	HOPPING Hop forward on 1 foot for 5 hops, then on other foot for 5 hops. Say, "Hop like I did."	2 Hops forward 5 hops on 1 foot, then 3–5 hops on other foot 1 Hops forward 1–4 hops on 1 foot, 1–2 hops on other foot 0 Hops in place, or foot fails to leave ground				
78	51–52	WALKING LINE BACKWARD **Taped line (4 in. × 8 ft.)** With toes touching heels and hands on hips, walk backward on line. Say, "Put your hands on your hips and walk backward touching your heels with your toes like I did. Try not to step off the line."	2 Walks backward 5 steps without stepping off line and with hands on hips and toes touching heels 1 Walks backward 2–4 steps without stepping off line and with hands on hips and toes touching heels 0 Takes less than 2 steps backward				
79	51–52	ROLLING FORWARD *(Crouching on edge of mat)* Demonstrate forward roll. Place child on edge of mat in crouching position. Say, "Turn a forward roll like I did."	2 Completes forward roll without turning more than 15 degrees to either side 1 Completes forward roll but turns more than 15 degrees to either side 0 Fails to complete forward roll				
80 Start: 59–62 months	51–52	GALLOPING Gallop 8–10 ft. (same foot leading). Say, "Gallop like I did."	2 Gallops 10 ft. with weight transferred smoothly and evenly; arms move freely in opposition to legs 1 Gallops 5–9 ft. with weight transferred smoothly and evenly; arms move freely in opposition to legs 0 Gallops less than 5 ft.				
81	53–54	JUMPING FORWARD **Taped line (2 in. × 2 ft.)** From taped starting line, demonstrate jumping forward using 2-footed takeoff and landing. Say, "Jump like I did as far as you can."	2 Jumps forward 36 in. using 2-footed takeoff and landing 1 Jumps forward 20–35 in. using 2-footed takeoff and landing 0 Jumps forward less than 20 in. or falls				

Item #	Age in Months	Item NAME, *Position*, and Description	Score Criteria	Administration 1	2	3	4
82	53–54	TURNING JUMP *(Standing with hands on hips, feet 2–4 in. on either side of line)* **Taped line (2 in. × 2 ft.)** With body not deviating more than 20 degrees from vertical, jump and turn 180 degrees. Land with feet opposite original position. Say, "Jump and turn in the air like I did."	2 Jumps and turns so feet land in opposite direction from starting position with hands on hips and body not deviating more than 20 degrees from vertical 1 Jumps and turns at least 90 degrees but less than 180 degrees with hands on hips and body not deviating more than 20 degrees from vertical 0 Turns less than 90 degrees				
83 Start: 63–71 months	53–54	HOPPING FORWARD **2 taped lines (2 in. × 2 ft.), 3 ft. apart** Hop on 1 foot from one line to other, change feet, and hop back to first line. Say, "Hop like I did." If necessary, remind child to change feet when hopping back.	2 Hops on 1 foot from one line to other, changes feet, and hops back to 1st line 1 Hops on 1 foot from one line to other, changes feet, and hops 1–2 hops toward 1st line 0 Hops in place or fails to hop to line				
84	57–58	JUMPING HURDLES **String (or rope) tied between 2 chair legs, 3 ft. apart, 10 in. off floor** (Tie loosely to prevent tripping.) Stand 6 in. away from and facing string. Using 2-footed takeoff and landing, jump over string. Say, "Jump over the string like I did."	2 Jumps over string without tripping using 2-footed takeoff and landing 1 Jumps over string without tripping using 1-footed takeoff and landing 0 Steps over string or jumps but remains on same side				
85	57–58	RUNNING SPEED AND AGILITY **2 taped lines (2 in. × 2 ft.), 10 ft. apart; empty soft drink can** Place can on one line. Have child stand just behind other line. Say, "When I say go, run as fast as you can, pick up the can, and bring it back across the starting line." (Allow 30 seconds of rest between trials.)	2 Completes cycle in 5 seconds or less without tripping or dropping can 1 Completes cycle in 6–10 seconds without tripping or dropping can 0 Takes more than 10 seconds to return to starting line				
86	57–58	SKIPPING Demonstrate skipping for 10 steps. Say, "Skip like I did."	2 Skips 8 steps maintaining balance, using opposing arm and leg movements, and using alternating feet 1 Skips 4–7 steps maintaining balance, using opposing arm and leg movements, and using alternating feet 0 Skips less than 4 steps or holds arms stiffly at sides				
87	59–60	JUMPING SIDEWAYS *(Standing, hands on hips, side to line)* **Taped line (2 in. × 2 ft.)** With feet together and without pausing, jump back and forth (sideways) over line for 3 left–right cycles. Say, "Jump across the line like I did."	2 Jumps back and forth 3 cycles with hands on hips, feet together, and without touching line or pausing between jumps 1 Jumps back and forth 1–2 cycles with hands on hips, feet together, and without touching line or pausing between jumps 0 Lands on line or pauses between jumps				
88	61–62	SKIPPING Demonstrate skipping 10 ft. Say, "Skip like I did."	2 Skips 10 ft. maintaining balance and rhythm, using opposing arm and leg movements, and using alternating feet 1 Skips 5–9 ft. maintaining balance and rhythm, using opposing arm and leg movements, and using alternating feet 0 Skips less than 4 ft. or holds arms stiffly at sides				
89	63–64	HOPPING SPEED **2 taped lines (2 in. × 2 ft.), 20 ft. apart** Place child behind starting line. Say, "Hop on 1 foot to the other line as fast as you can."	2 Hops 20 ft. in 6 seconds or less without losing balance or letting free foot touch floor 1 Hops 20 ft. in 7–10 seconds without losing balance or letting free foot touch floor 0 Hops less than 20 ft. or requires more than 10 seconds				

Item #	Age in Months	Item NAME, *Position*, and Description	Score Criteria	Administration 1	2	3	4
Object Manipulation							
1 Start: 12–16 months	12	CATCHING BALL *(Sitting, legs spread apart facing you, you and child sitting 3 ft. apart)* Roll **ball** from between your legs to child. Say, "Catch the ball."	2 Corrals ball with arms and/or hands without losing balance 1 Corrals ball, but loses balance 0 Misses ball				
2	13	ROLLING BALL *(Sitting, legs spread apart facing you, you and child sitting 3 ft. apart)* Roll **ball** from between your legs to child. Place ball on floor between child's knees. Say, "Roll the ball to me."	2 Rolls ball 3 ft. forward using hand/arm contact 1 Rolls ball 2–3 ft. forward using hand/arm contact 0 Rolls ball forward 2 ft. or less				
3	13	FLINGING BALL *(Standing in an open area)* Give **tennis ball** to child and stand 5 ft. away. Extend your hands to child and say, "Throw the ball to me."	2 Throws ball in any direction by extending arm at shoulder or elbow 1 Releases ball without extending arm at elbow 0 Holds ball or lays it down				
4 Start: 17–20 months	15–16	KICKING BALL *(Standing in an open area)* Kick a stationary **ball** so that it travels 3 ft. forward. Place ball 6 in. in front of child and say, "Kick the ball like I did."	2 Lifts foot and contacts ball 1 Lifts foot and attempts to kick ball 0 Fails to lift foot				
5	15–16	THROWING BALL *(Standing in an open area)* Give **tennis ball** to child and stand 5 ft. away. Say, "Throw the ball to me."	2 Throws ball by extending arm at shoulder or elbow while maintaining balance 1 Throws ball using an extended arm, but loses balance 0 Drops ball				
6 Start: 21–28 months	19–20	KICKING BALL *(Standing in an open area)* Kick a stationary **ball** so it travels 3 ft. forward. Place ball 6 in. in front of child and say, "Kick the ball like I did."	2 Kicks ball forward 3 ft. without it deviating more than 45 degrees to either side of midline 1 Kicks ball forward 3 ft. but it deviates more than 45 degrees from midline 0 Ball travels less than 3 ft.				
7	19–20	THROWING BALL—Overhand *(Standing in an open area)* Demonstrate throwing **tennis ball** overhand at least 3 ft. forward. Give ball to child. Say, "Throw the ball as far as you can."	2 Throws ball forward 3 ft. in the air 1 Throws ball forward 1–2 ft. in the air 0 Drops ball or throws in direction other than forward				
8	23–24	THROWING BALL—Underhand *(Standing in an open area)* Demonstrate throwing **tennis ball** underhand at least 5 ft. Give ball to child. Say, "Throw the ball as far as you can."	2 Throws ball forward 3 ft. in the air 1 Throws ball forward 1–2 ft. in the air 0 Drops ball or throws in any direction other than forward				
9 Start: 29–38 months	23–24	KICKING BALL *(Standing in an open area)* Kick stationary **ball** so it travels 3 ft. forward. Place ball 6 in. in front of child and say, "Kick the ball like I did."	2 Kicks ball forward 3 ft. without it deviating more than 20 degrees to either side of midline 1 Kicks ball forward 3 ft. but it deviates more than 20 degrees from midline 0 Ball travels less than 3 ft. and deviates more than 20 degrees from midline				
10	25–26	CATCHING BALL *(Standing in an open area)* Stand 5 ft. in front of child. Say, "Catch the ball." Toss **ball** so that it arrives at chest height, contacting child's outstretched arms.	2 Presents extended arms directly in front, palms upward or facing each other; attempts to secure ball by bending arms toward chest (may or may not catch ball) 1 Presents extended arms directly in front, palms upward or facing each other; arms remain straight when contacted by ball 0 Turns away from thrown ball				

Item #	Age in Months	Item NAME, *Position*, and Description	Score Criteria	Administration 1	2	3	4
11	27–28	THROWING BALL—Overhand *(Standing in an open area)* Demonstrate throwing **tennis ball** overhand at least 7 ft. Give ball to child. Stand 8 ft. away and say, "Throw me the ball."	2 Initiates throw by moving arm upward and back; ball travels 7 ft. in the air 1 Initiates throw by moving arm down and back, sideways and back, upward, or downward; ball travels 6 ft. or less in the air 0 Drops ball or throws in any direction other than forward				
12 Start: 39–46 months	29–30	THROWING BALL—Underhand *(Standing in an open area)* Demonstrate throwing the **tennis ball** underhand at least 7 ft. forward. Give ball to child. Stand 8 ft. away and say, "Throw me the ball."	2 Initiates throw by moving arm down and back; ball travels forward 7 ft. in the air 1 Initiates throw by moving arm sideways, upward, or forward; ball travels less than 7 ft. in the air 0 Drops ball or throws in any direction other than forward				
13	29–30	KICKING BALL *(Standing in an open area)* Kick stationary **ball** so that it travels at least 6 ft. forward. Place ball 6 in. in front of child and say, "Kick the ball hard like I did."	2 Kicks ball forward 6 ft. using opposing arm and leg movements and initiating kick by extending leg back with bent knee 1 Kicks ball forward 2–6 ft. using opposing arm and leg movements and initiating kick by extending leg back with bent knee 0 Fails to use opposing arm and leg movements or ball travels less than 2 ft.				
14	33–34	CATCHING BALL *(Standing in an open area)* Stand 5 ft. in front of child. Say, "Catch the ball." Toss **ball** so that it arrives at chest height, contacting child's outstretched arms.	2 Catches ball with hands and arms extended 1 Brings arms toward chest in effort to catch after ball contacts hands and arms 0 Turns away from ball or arms remain stationary				
15 Start: 47–52 months	39–40	THROWING BALL—Overhand *(Standing in an open area)* Demonstrate throwing **tennis ball** overhand at least 10 ft. Give ball to child. Stand 11 ft. away and say, "Throw the ball as far as you can."	2 Throws ball forward 10 ft. by moving arm up and back using upper trunk rotation, arms and legs moving in opposition 1 Throws ball forward 3–9 ft. by moving arm up and back or sideways and back using upper trunk rotation, arms and legs moving in opposition 0 Throws ball forward less than 3 ft. or throws ball by moving arm down and back with trunk remaining stationary				
16	39–40	HITTING TARGET—Underhand *(Standing 5 ft. from wall)* From 5 ft. away, toss **tennis ball** underhand to **2-ft. target taped on wall (2 ft. above floor)**. Say, "Throw the ball and hit the target like I did."	2 Hits target 2 of 3 trials using an underhand toss 1 Hits target 1 of 3 trials using an underhand toss 0 Fails to hit target using underhand toss				
17	41–42	CATCHING BALL *(Standing in an open area)* Stand 5 ft. in front of child. Say, "Catch the ball." Toss **ball** so that it arrives at chest height.	2 Catches ball with hands (securing it to chest if necessary) with arms bent 45–90 degrees at the elbows and palms up or facing each other 1 Catches ball by encircling it with arms and hands, then pulling ball to chest (arms may be held out straight in preparation to catch) 0 Fails to catch ball				
18	43–44	HITTING TARGET—Overhand *(Standing 5 ft. from wall)* From 5 ft. away, toss **tennis ball** twice overhand to **2-ft. target taped on wall (2 ft. above floor)**. Say, "Throw the ball and hit the target like I did."	2 Hits target 2 of 3 trials using an overhand toss 1 Hits target 1 of 3 trials using an overhand toss 0 Fails to hit target using overhand toss				

Item #	Age in Months	Item NAME, *Position*, and Description	Score Criteria	Administration 1	2	3	4
19 Start: 53–64 months	45–46	THROWING BALL—Underhand *(Standing in an open area)* Demonstrate throwing **tennis ball** underhand at least 10 ft. Give ball to child. Stand about 12 ft. away and say, "Throw the ball as far as you can."	2 Throws ball 10 ft. using upper trunk rotation, arms and legs moving in opposition, and initiating the throw by moving arm down and back 1 Throws ball 3–9 ft. using upper trunk rotation, arms and legs moving in opposition, and initiating the throw by moving arm down and back or sideways and back 0 Throws by moving arm up and back (trunk remains stationary) or ball travels less than 3 ft.				
20 Start: 65–71 months	51–52	HITTING TARGET—Overhand *(Standing 12 ft. from wall)* From 12 ft. away, toss **tennis ball** overhand to **2-ft. target taped on wall (2 ft. above floor)**. Say, "Throw the ball and hit the target like I did."	2 Hits target 2 of 3 trials using an overhand toss 1 Hits target 1 of 3 trials using an overhand toss 0 Fails to use overhand toss or to hit target				
21	51–52	BOUNCING BALL *(Standing 5 ft. from wall)* Using 1 hand, bounce **tennis ball** so it bounces once and then hits wall. Give ball to child and say, "Bounce the ball like I did."	2 Bounces ball to wall so it hits floor once and then hits wall 1 Bounces ball to wall so it hits floor more than once before hitting wall 0 Throws ball that hits wall first or misses wall after bounce				
22	51–52	CATCHING BALL *(Standing in an open area)* Stand 5 ft. in front of child. Say, "Catch the ball." Toss **tennis ball** in a 45-degree arc so it arrives at child's hands.	2 Catches ball on 2 of 3 trials with arms bent and using only hands 1 Catches ball on 1 of 3 trials with arms bent and using only hands 0 Fails to catch ball				
23	68–72	KICKING BALL *(Standing in an open area)* Kick a stationary **ball** so that it travels in the air for at least 12 ft. Place ball 6 in. in front of child's feet and say, "Kick the ball like I did."	2 Kicks ball so it travels 12 ft. in the air using opposing arm and leg movements and initiating kick by extending leg back with bent knee 1 Kicks ball so it travels 6–11 ft. in the air using opposing arm and leg movements and initiating kick by extending leg back with bent knee 0 Kicks ball that travels less than 6 ft. in air or fails to use opposing arm and leg movements				
24	68–72	CATCHING BOUNCED BALL Bounce **tennis ball** on floor once and catch it with 1 hand. Say, "Bounce and catch the ball like I did."	2 Bounces and catches ball on 2 of 3 trials 1 Bounces and catches ball on 1 of 3 trials 0 Fails to catch ball				
Fine Motor Scales							
Grasping							
1 Start: 1–2 months	0	GRASPING REFLEX *(Lying on back)* Stimulate child's palm by inserting your index finger into thumb side of palm.	2 Closes fingers in tight grasp around examiner's finger 1 Bends fingers loosely around examiner's finger 0 Extends fingers, fails to bend them				
2	0	GRASPING CLOTH *(Lying on back)* Spread **washcloth** over your forearm. Place child's hand on top of washcloth.	2 Grasps cloth in hand 1 Scratches at cloth but fails to grasp it 0 Extends fingers, fails to grasp cloth				

Item #	Age in Months	Item NAME, *Position*, and Description	Score Criteria	Administration 1	2	3	4
3	0	RELEASING RATTLE—Disappearing Reflex *(Lying on back)* Place **rattle** in child's hand. After child holds rattle for 5 seconds, observe amount of time before release.	2 Drops rattle within 3 additional seconds 1 Drops rattle within 4–5 additional seconds 0 Drops rattle after 5 additional seconds				
4	2	GRASPING RATTLE *(Lying on back)* Lightly touch child's palm with **rattle**. Say, "Get your rattle."	2 Grasps rattle 1 Touches rattle with fingers but fails to grasp it 0 Fails to extend fingers				
5 Start: 3–5 months	2	HOLDING RATTLE *(Lying on back)* Place **rattle** in child's hand.	2 Holds rattle for 30 seconds 1 Holds rattle for 15–29 seconds 0 Holds rattle for less than 15 seconds				
6	3	MANIPULATING RATTLE *(Lying on back)* Shake **rattle** and place it in child's hand. Say, "Shake your rattle."	2 Moves rattle 15 degrees 1 Moves rattle 5–14 degrees 0 Moves rattle 4 degrees or less				
7	4	GRASPING RATTLE *(Sitting on lap, facing table)* Place **rattle** on table within 3 in. of child's hand. Say, "Get your rattle."	2 Grasps rattle 1 Touches rattle 0 Extends arm toward rattle				
8 Start: 6 months	5	PULLING STRING *(Lying on stomach)* Place **toy on a string** so string is at midline between child's hands. Say, "Get the toy."	2 Grasps string, pulls it, and obtains toy 1 Grasps, touches, or pulls string 0 Looks at toy				
9	5	SECURING PAPER *(Sitting on lap, facing table)* Place **8.5 × 11 in.** paper within 3 in. of child's hand. Say, "Get the paper."	2 Secures paper by pulling with open hand or by wrinkling it 1 Touches paper 0 Extends hand toward paper				
10	5	GRASPING CUBE *(Sitting on lap, facing table)* Place **cube** on table within 3 in. of child's hand. Say, "Get the block."	2 Grasps cube for 15 seconds 1 Touches cube for 15 seconds 0 Extends hand to cube but fails to touch				
11 Start: 7–9 months	6	GRASPING CUBE *(Sitting on lap, facing table)* Place **cube** on table within 3 in. of child's hand. Say, "Get the block." Observe how child picks up cube.	2 Grasps cube with 4th and 5th fingers and palm, or grasps cube with thumb and 1st and 2nd fingers 1 Grasps cube with little finger and palm 0 Grasps cube with whole fist				
12	6	SHAKING RATTLE *(Sitting on lap, facing table)* Place **rattle** in child's hand. Say, "Shake your rattle."	2 Holds and moves rattle for 60 seconds 1 Holds and moves rattle for 11–59 seconds 0 Moves rattle for 10 seconds or less				
13	7	SHAKING RATTLE *(Sitting on lap, facing table)* Shake **rattle** back and forth through a 90-degree arc 3 times. Place it on table in front of child. Say, "Shake the rattle."	2 Moves rattle 3 times through 90-degree arcs 1 Moves rattle 3 times through 45- to 89-degree arcs 0 Moves rattle less than 45 degrees or arcs less than 3 times				
14	7	GRASPING CUBE *(Sitting on lap, facing table)* Place **cube** on table within 3 in. of child's hand. Say, "Get the block." Observe how child picks up cube.	2 Grasps cube with thumb and 1st and 2nd fingers with space visible between cube and palm 1 Grasps cube with 1st and 2nd fingers and heel of palm (no space between cube and palm) 0 Grasps cube with whole fist				
15 Start: 10–12 months	8	GRASPING PELLETS *(Sitting on lap, facing table)* Place **2 food pellets** on table within child's reach. Say, "Get all the food."	2 Grasps both pellets at once using a raking motion with fingers 1 Grasps 1 pellet using a raking motion with fingers 0 Touches pellet(s)				

Item #	Age in Months	Item NAME, *Position,* and Description	Score Criteria	Administration 1	2	3	4
16	8	MANIPULATING PAPER *(Sitting on lap, facing table)* Cut **8.5 × 11 in. sheet of paper** in half. Place half on table. Say, "Watch me crumple the paper." Crumple paper in 1 hand. Place other half of paper within 3 in. of child's hand. Say, "Crumple the paper like I did."	2 Crumples paper with palm(s) (1 or 2 hands) 1 Wrinkles paper with fingers 0 Touches or pulls paper				
17	8	GRASPING PELLETS *(Sitting on lap, facing table)* Place **2 food pellets** on table within child's reach. Say, "Get all the food."	2 Grasps 2 pellets using raking motion, but with thumb against side of curled index finger, or grasps 1 pellet with thumb and pad of index finger 1 Grasps 1 pellet with thumb and index finger 0 Grasps both pellets at once using a raking motion				
18 Start: 13–20 months	11	GRASPING PELLETS *(Sitting on lap, facing table)* Place **2 food pellets** on table within child's reach. Say, "Get all the food."	2 Grasps 1 or 2 pellets with pad of thumb and pad of index finger; hand, wrist, and arm off table 1 Grasps 1 or 2 pellets with pad of thumb and pad of index finger; arm on table 0 Grasps pellet using grasp other than thumb and pad of index finger				
19	11	GRASPING CUBE *(Sitting on lap, facing table)* Place **cube** on table within 3 in. of child's hand. Say, "Get the block." Observe how child picks up cube.	2 Grasps cube with thumb opposed to 1st and 2nd finger pads with space visible between cube and palm and with hand approaching from top 1 Grasps cube with thumb and 1st and 2nd finger pads with hand approaching from side (but not in contact with table) 0 Grasps cube with whole fist				
20 Start: 21–34 months	13	GRASPING CUBES *(Sitting on lap, facing table)* Place **2 cubes** side by side. Pick up both cubes with 1 hand. Place cubes on table and say, "Pick up both blocks with 1 hand like I did."	2 Grasps both cubes with 1 hand and holds them for 3 seconds 1 Grasps both cubes with 1 hand and holds them for less than 3 seconds 0 Grasps 1 cube				
21 Start: 35–71 months	15–16	GRASPING MARKER *(Sitting at table)* Place **paper and marker** by child's hand on table. Say, "Make a mark." Observe how child holds marker.	2 Grasps marker with thumb and 1st finger toward paper and remaining fingers around marker 1 Grasps marker with thumb up and little finger toward paper 0 Fails to grasp marker				
22	41–42	GRASPING MARKER *(Sitting at table)* Place **paper and marker** by child's hand on table. Say, "Make a mark." Observe how child holds marker.	2 Grasps marker with thumb and pad of index finger; other 3 fingers are secure against palm; upper portion of marker rests between thumb and index finger; child moves hand as unit when drawing 1 Grasps marker with thumb and pad of index finger; upper portion of marker rests between thumb and index finger 0 Grasps marker with thumb and 1st finger				
23	41–42	UNBUTTONING BUTTONS *(Sitting at table)* Place **button strip** on table. Say, "Unbutton these as fast as you can."	2 Unbuttons 3 buttons in 75 seconds or less 1 Unbuttons 3 buttons in 76 seconds or more 0 Attempts to unbutton buttons				
24	47–48	BUTTONING BUTTON *(Sitting at table)* Place **button strip** on table. Unbutton the buttons. Point to an end button and say, "Button and unbutton this one as fast as you can."	2 Buttons and unbuttons 1 button in 20 seconds or less 1 Buttons and unbuttons 1 button in 21 seconds or more 0 Holds both strips together				

Item #	Age in Months	Item NAME, *Position*, and Description	Score Criteria	Administration 1	2	3	4
25	49–50	GRASPING MARKER *(Sitting at table)* Place **paper and marker** by child's hand on table. Say, "Make a mark." Observe how child holds marker.	2 Grasps marker between thumb and pad of index finger; marker rests on first joint of middle finger 1 Grasps marker between thumb and pad of index finger; marker rests on first knuckle or pad of middle finger 0 Grasps marker with thumb and 1st finger				
26	53–54	TOUCHING FINGERS At the rate of 1 touch per second, beginning with index finger, touch each finger in succession to thumb. Say, "Touch like I did as fast as you can."	2 Touches each finger to thumb within 8 seconds 1 Touches each finger to thumb in 9–12 seconds 0 Touches each finger in 13 seconds or more				
		Visual-Motor Integration					
1 Start: 1–2 months	1	TRACKING RATTLE *(Lying on back)* Hold **rattle** 12 in. from child's nose. Slowly move rattle in a 90-degree arc to one side (almost to the surface). Return to midline and repeat procedure to other side.	2 Tracks rattle 90 degrees to each side of midline 1 Tracks rattle less than 90 degrees to either or both sides 0 Fixates eyes on rattle for 3 seconds or less				
2	1	TRACKING RATTLE—Side *(Lying on back, head turned to side)* Hold **rattle** 12 in. from child's nose. Slowly move rattle in arc to midline. Repeat with child's head turned to other side.	2 Tracks rattle to midline on both sides 1 Tracks rattle to midline on 1 side only 0 Head remains turned to side				
3	1	PLACING HAND *(Sitting on lap, facing away from table)* Using an upward movement, gently brush the back of child's hand against table edge.	2 Places open hand on table 1 Places fisted hand on table 0 Fails to place hand on table				
4 Start: 3 months	2	PERCEIVING RATTLE *(Lying on back)* Hold **rattle** 12 in. from child's nose. Slowly lower rattle to within 1 in. of nose.	2 Turns head more than 10 degrees 1 Turns head less than 10 degrees 0 Head remains stationary				
5	2	REGARDING HANDS *(Lying on back)* Hold child's hands and wave them in front of face. If child's arms are too short, turn child's head to side and wave 1 hand.	2 Looks at hands for 3 seconds 1 Looks at hands for 1–2 seconds 0 Eyes remain fixed or averted				
6	2	TRACKING BALL—Left to Right *(Sitting on lap, facing table, examiner sits with side to table)* Roll **tennis ball** on table from left to right. Say, "Watch the ball."	2 Tracks ball beyond midline 1 Tracks ball to midline 0 Head remains still				
7 Start: 4 months	2	TRACKING BALL—Right to Left *(Sitting on lap, facing table, examiner sits with side to table)* Roll **tennis ball** on table from right to left. Say, "Watch the ball."	2 Tracks ball beyond midline 1 Tracks ball to midline 0 Head remains still				
8	2	TRACKING RATTLE *(Lying on back with head turned to side)* Hold **rattle** 12 in. from child's nose. Slowly move rattle in a 110-degree arc through midline. Return rattle to side position. Repeat with child's head turned to other side.	2 Tracks rattle through midline on both sides 1 Tracks rattle through midline on one side only 0 Tracks rattle to midline or less				
9 Start: 5–6 months	3	EXTENDING ARMS *(Lying on back)* Shake **rattle** and then hold it 12 in. above child's chest. Say, "Get your rattle."	2 Extends straight arms toward rattle 1 Extends bent arms (90-degree angle or less) toward rattle or extends arms in any direction other than toward rattle 0 Arms remain in same position or continue in same activity				

Item #	Age in Months	Item NAME, *Position*, and Description	Score Criteria	Administration 1	2	3	4
10	4	APPROACHING MIDLINE *(Lying on back)* Dangle **toy on a string** 12 in. above child's chest. Say, "Get the toy."	2 Moves hand within 4 in. of midline while reaching for toy 1 Moves hand in any direction except toward midline 0 Fails to move hand				
11 Start: 7 months	4	FINGERING HANDS *(Lying on back)* Hold child's arms between wrist and elbow and bring child's fingers together at midline; then release your hands.	2 Engages fingers in mutual touching for 5 seconds 1 Engages fingers in mutual touching for 3–4 seconds 0 Engages fingers in mutual touching for 0–2 seconds				
12	6	BRINGING HANDS TOGETHER *(Sitting on lap, facing table)* Place **cube** in child's hand. Say, "Play with your block."	2 Brings hands together and secures cube for 15 seconds 1 Brings hands together and secures cube for 1–14 seconds 0 Fails to bring hands together				
13 Start: 8 months	6	EXTENDING ARM *(Lying on back)* Shake and hold **rattle** 12 in. from child's nose. Say, "Get your rattle."	2 Extends arm toward rattle with elbow angle greater than 90 degrees while other arm remains stationary 1 Extends arm toward rattle with elbow angle less than 90 degrees while other arm remains stationary 0 Extends both arms toward rattle				
14	6	RETAINING CUBES *(Sitting on lap, facing table)* **2 cubes** Place **cube** on table and say, "Get the block." After child picks up cube, place **2nd cube** on table. Say, "Get this one, too."	2 Picks up 2nd cube and retains both for 5 seconds 1 Picks up 2nd cube and retains both for less than 5 seconds 0 Picks up only 1 cube				
15	7	TRANSFERRING CUBE *(Sitting on lap, facing table)* **2 cubes** Place **cube** in child's hand. Place **2nd cube** on table within reach of hand already holding cube and as far away as possible from empty hand. Say, "Get this one, too."	2 Transfers cube to other hand and picks up 2nd cube with original hand 1 Transfers cube to other hand and extends either hand to 2nd cube 0 Reaches for 2nd cube without transferring 1st cube				
16 Start: 9 months	7	TOUCHING PELLET *(Sitting on lap, facing table)* Place **food pellet** on table within child's reach. Say, "Get the food."	2 Touches pellet with finger(s) 1 Touches pellet with palm or touches table near pellet 0 Extends hand toward pellet				
17	7	BANGING CUP *(Sitting on lap, facing table)* Bang **cup** 3 times on table; then set it down. Say, "Bang the cup."	2 Bangs cup 3 times 1 Bangs cup 1–2 times 0 Picks up cup but fails to bang				
18 Start: 10 months	8	POKING FINGER *(Sitting on lap, facing table)* Put **pegboard** on table in front of child. Demonstrate poking index finger into hole. Say, "You do it."	2 Pokes finger in hole 1 Places finger within ⅛ in. of hole 0 Touches table or pegboard				
19	8	REMOVING PEGS *(Sitting on lap, facing table)* Place **pegboard** with **3 pegs** loosely inserted in front of child. Say, "Get the pegs."	2 Removes 1 or more pegs 1 Attempts to remove peg 0 Touches pegs				

Item #	Age in Months	Item NAME, *Position*, and Description	Score Criteria	Administration 1	2	3	4
20	9	COMBINING CUBES *(Sitting on lap, facing table)* **2 cubes** Place **cube** in child's left hand. Place **2nd cube** near right hand. Say, "Get this one, too, and bang them together." Demonstrate if necessary.	2 Secures 2nd cube and brings cubes together at midline 1 Takes 2nd cube but fails to bring them together at midline 0 Fails to secure 2nd cube				
21	9	CLAPPING HANDS *(Sitting facing examiner)* Clap your hands while you say, "Do pat-a-cake" or "Clap your hands."	2 Claps hands 3 times 1 Claps hands 1–2 times 0 Brings hands together				
22 Start: 11 months	10	RETAINING CUBES *(Sitting on lap, facing table)* **3 cubes** Place **cube in each of child's hands.** After child has retained cubes for 3 seconds, place **3rd cube** on table. Say, "Get this one, too. Hold all the blocks."	2 Extends hand toward 3rd cube while holding both cubes 1 Drops a cube while extending hand to 3rd cube 0 Looks at cube				
23	10	MANIPULATING STRING *(Sitting on lap, facing table)* **Toy on a string** Place **string** on table with **toy** below table and out of sight. Say, "Get the string."	2 Secures string and pulls it 1 Pats string 0 Touches string				
24 Start: 12 months	10	REMOVING PEGS *(Sitting on lap, facing table)* Place **pegboard** with **3 pegs** loosely inserted in front of child. Say, "Take out the pegs."	2 Removes 3 pegs 1 Removes 2 pegs 0 Removes 0–1 peg				
25	10	RELEASING CUBE *(Sitting on lap, facing table)* Place **cube** in child's hand. Say, "Drop the block in my hand." Hold your hand 6 in. below and to the side of child's hand.	2 Releases cube into examiner's hand 1 Drops cube to table 0 Retains cube				
26 Start: 13 months	11	REMOVING SOCKS *(Sitting on floor)* Remove child's shoes and say, "Take off your **socks**."	2 Removes both socks 1 Removes 1 sock 0 Attempts to remove a sock or touches socks				
27	11	PLACING PELLET *(Sitting on lap, facing table)* Place **food pellet and cup** on table. Point to pellet and say, "Put it in the cup."	2 Grasps pellet with thumb and index finger and drops it into cup 1 Grasps pellet with thumb and index finger and extends hand toward cup 0 Grasps pellet				
28	11	PLACING CUBES *(Sitting on lap, facing table)* Place **7 cubes and cup** on table. Say, "Put the blocks in the cup."	2 Places 3–7 cubes in cup 1 Places 1–2 cubes in cup 0 Fails to place any cubes in cup				
29 Start: 14 months	12	TURNING PAGES *(Sitting on lap or in a safe seated position, facing table)* Place **book with thick cover and thick pages** on table. Say, "Open the book."	2 Opens book 1 Attempts to open book 0 Pats book				
30	12	STIRRING SPOON *(Sitting on lap or in a safe seated position, facing table)* Demonstrate stirring **spoon in cup**. Place spoon next to cup. Say, "Stir with the spoon."	2 Stirs spoon in cup 1 Moves spoon up and down in cup or puts spoon in cup 0 Secures spoon				
31 Start: 15–16 months	12	REMOVING PELLETS *(Sitting on lap or in a safe seated position, facing table)* Give **bottle (without cap) with food pellet inside** and say, "Get it out."	2 Turns bottle and dumps out pellet 1 Attempts to dump out pellet 0 Holds bottle				

Item #	Age in Months	Item NAME, *Position*, and Description	Score Criteria	Administration 1	2	3	4
32	13	PLACING CUBES *(Sitting on lap or in a safe seated position, facing table)* Place **7 cubes and cup** on table. Say, "Put the blocks in the cup."	2 Places 7 cubes in cup 1 Places 4–6 cubes in cup 0 Places 0–3 cubes in cup				
33	13	PLACING PEGS *(Sitting on lap or in a safe seated position, facing table)* Place **pegboard** on table and **3 pegs** between pegboard and child. Say, "Put the pegs in the board."	2 Places 3 pegs in pegboard 1 Places 1–2 pegs in pegboard 0 Picks up pegs				
34	13	TAPPING SPOON *(Sitting on lap or in a safe seated position, facing table)* Demonstrate using horizontal motion to tap **cup** with **spoon**. Place spoon on table. Say, "You do it."	2 Taps cup with horizontal motion 1 Taps cup with vertical motion 0 Picks up spoon				
35	13	INSERTING SHAPES *(Sitting on lap, facing table)* Place **formboard** on table. Place **shapes** between child and board under holes in which they belong. Point to shapes and then to holes and say, "Put the shapes in the board."	2 Places 1 shape into correct hole 1 Places 1 shape partially into correct hole 0 Picks up shape and puts it on board				
36 Start: 17–18 months	14	PLACING PELLET *(Sitting on lap or in a safe seated position, facing table)* Place **bottle** and **4 food pellets** on table. Pick up pellet and put it in bottle. Point to another pellet and say, "Put it in the bottle."	2 Puts pellet in bottle 1 Attempts to put pellet in bottle 0 Picks up pellet				
37	14	SCRIBBLING *(Sitting on lap or in a safe seated position, facing table)* **2 markers and 2 sheets of paper** Draw 2 vertical lines about 3 in. long. Place 2nd sheet of **paper** and **marker** on table. Say, "Do what I did."	2 Makes at least 1 scribble more than 1 in. long 1 Makes scribble less than 1 in. long 0 Touches paper with marker				
38 Start: 19–22 months	15–16	BUILDING TOWER *(Sitting on lap, facing table)* **6 cubes** Say, "Watch me build a tower." Build tower of **3 cubes**. Leave tower standing. Give child **3 cubes** and say, "You build a tower."	2 Stacks 2–3 cubes 1 Attempts to stack 2 cubes 0 Grasps cube				
39	17–18	INSERTING SHAPES *(Sitting on lap, facing table)* Place **formboard** on table. Place **3 shapes** between child and board but not next to correct holes. Point to shapes and then to holes and say, "Put the shapes in the board."	2 Places 2 shapes into correct holes 1 Places 1 shape into correct hole and 2nd shape partially into correct hole 0 Places 1 shape into correct hole				
40 Start: 23–26 months	19–20	BUILDING TOWER *(Sitting on lap or in a safe seated position, facing table)* **10 cubes** Say, "Watch me build a tall tower." Build tower of **5 cubes**. Leave tower standing. Give child **5 cubes** and say, "You build a tall tower."	2 Stacks 4–5 cubes 1 Stacks 3 cubes 0 Stacks 2 cubes				
41	19–20	TURNING PAGES *(Sitting on lap, facing table)* Place **book with thick cover and thick pages** on table. Say, "Look at the book."	2 Turns 3 pages, 1 at a time 1 Turns 2 pages singly or turns 2 or more pages together 0 Opens book				

Item #	Age in Months	Item NAME, *Position*, and Description	Score Criteria	Administration 1	2	3	4
42	19–20	INSERTING SHAPES *(Sitting on lap, facing table)* Place **formboard** on table. Place **3 shapes** between child and board but not next to correct holes. Point to shapes and then to holes and say, "Put the shapes in the board."	2 Places 3 shapes into correct holes 1 Places 2 shapes into correct holes and 3rd shape partially into correct hole 0 Places 2 shapes into correct holes				
43 Start: 27–28 months	21–22	BUILDING TOWER *(Sitting on lap or in a safe seated position, facing table)* Say, "Watch me build a tall tower." Build a tower of **6 cubes**. Let tower stand for a few seconds, then knock it down. Give child **6 cubes** and say, "You build a tall tower."	2 Stacks 6 cubes 1 Stacks 5 cubes 0 Stacks 4 cubes				
44	23–24	IMITATING VERTICAL STROKES *(Sitting on lap, facing table)* **2 markers and 2 sheets of paper** Draw 2 vertical lines about 3 in. long. Place 2nd sheet of **paper** and **marker** on table. Say, "Draw a line up and down like I did."	2 Makes stroke 2 in. long and within 20 degrees of vertical 1 Makes stroke 2 in. long and within 21–45 degrees of vertical 0 Makes stroke less than 2 in. long or more than 45 degrees of vertical				
45 Start: 29–30 months	25–26	REMOVING TOP *(Sitting at a table)* Place **food pellet** in **bottle** and screw on **lid**. Give bottle to child and say, "Get the food."	2 Removes lid 1 Attempts to remove lid 0 Shakes bottle				
46	25–26	BUILDING TOWER *(Sitting at a table)* Say, "Watch me build a tall tower." Build a tower of **10 cubes**. Let tower stand for few seconds, then knock it down. Give child **10 cubes** and say, "You build a tall tower."	2 Stacks 8 cubes 1 Stacks 7 cubes 0 Stacks 6 cubes				
47	25–26	SNIPPING WITH SCISSORS *(Sitting at a table)* Cut edge of a piece of paper in 3 places. Give **paper** and **scissors** to child. Say, "You cut the paper."	2 Cuts paper in 1 place 1 Opens scissors and attempts to cut 0 Touches paper with scissors				
48 Start: 31–32 months	27–28	IMITATING HORIZONTAL STROKES *(Sitting at a table)* **2 markers and 2 sheets of paper** Draw 2 horizontal lines 3 in. long. Place 2nd sheet of **paper** and **marker** on table. Say, "Draw a line like I did."	2 Makes stroke 2 in. long and within 20 degrees of horizontal 1 Makes stroke 2 in. long and within 21–45 degrees of horizontal 0 Makes stroke less than 2 in. long or more than 45 degrees from horizontal				
49	27–28	STRINGING BEADS *(Sitting at a table)* **Lace and 6 square beads** String **2 beads** on **lace**. Hand **lace** to child. Put **4 beads** on table and say, "String the beads like I did."	2 Strings 2 beads 1 Strings 1 bead 0 Attempts to string a bead				
50 Start: 33–34 months	27–28	FOLDING PAPER *(Sitting at a table)* **8.5 × 11 in. sheet of paper, cut in half** Fold piece of paper in half and leave it where child can see it. Give child other piece of paper and say, "Fold it like mine."	2 Bends paper, producing a crease 1 Crumples paper 0 Touches paper				
51	29–30	BUILDING TRAIN *(Sitting at a table)* **8 cubes** Build train as pictured in Guide to Item Administration. Push train across table making train sounds. Leave it where child can see it. Put **4 cubes** in front of child and say, "Make a train like mine."	2 Aligns 3 cubes and positions 4th cube on top at one end 1 Aligns 3 cubes but incorrectly positions top cube 0 Aligns 2 cubes				

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52 Start: 35–38 months	29–30	STRINGING BEADS *(Sitting at a table)* **Lace and 6 square beads** String **2 beads** on **lace**. Hand **lace** to child. Put **4 beads** on table and say, "String all of these beads like I did."	2 Strings 4 beads 1 Strings 3 beads 0 Strings 2 beads				
53	29–30	BUILDING TOWER *(Sitting at a table)* Say, "Watch me build a tower." Build tower of **5 cubes**. Let tower stand for a few seconds, then knock it down. Give child **10 cubes** and say, "Build a tall tower using as many blocks as you can."	2 Stacks 10 cubes 1 Stacks 9 cubes 0 Stacks less than 9 cubes				
54	31–32	BUILDING BRIDGE *(Sitting at a table)* Build bridge with **3 cubes** as pictured in the Guide to Item Administration and leave it standing. Put **3 cubes** in front of child and say, "Build a bridge like mine."	2 Builds bridge as illustrated 1 Builds bridge with bottom 2 cubes touching or top cube out of position 0 Stacks cubes				
55 Start: 39–42 months	33–34	COPYING CIRCLE *(Sitting at a table)* Place **paper, marker,** and **card with circle** on table. Say, "Draw a circle."	2 Draws circle with end points within ½ in. of each other 1 Draws circle with end points ½ to 1 in. of beginning point; circle is at least ¾ complete 0 End points are more than 1 in. apart or circle is less than ¾ complete				
56	35–36	BUILDING WALL *(Sitting at a table)* **8 cubes** Build **4-cube** wall as pictured in Guide to Item Administration and leave standing. Place **4 cubes** in front of child and say, "Build a wall like mine."	2 Builds wall as illustrated or 2 towers touching 1 Builds two 2-cube towers with space between the towers 0 Builds single tower				
57 Start: 43–46 months	37–38	CUTTING PAPER *(Sitting at a table)* Cut piece of **8.5 × 11 in. paper** in half. Give **1 piece of paper** and **scissors** to child. Say, "Cut the paper like I did."	2 Cuts paper into 2 pieces 1 Cuts paper ¾ or less across 0 Snips with scissors				
58	39–40	LACING STRING *(Sitting at a table)* **Lacing strip and lace** Say, "Watch me lace." Lace down through 1st hole, up through 2nd hole. Lace string through 3 holes. Show strip to child, then remove lace and give to child. Say, "You do it like I did."	2 Laces 3 holes 1 Laces 2 holes 0 Puts lace through 0–1 hole				
59	39–40	COPYING CROSS *(Sitting at a table)* Place **paper, marker,** and **card with cross** on table. Say, "Draw lines just like these that cross in the middle."	2 Draws intersecting lines that are within 20 degrees of perpendicular 1 Draws intersecting lines that are more than 20 degrees from perpendicular 0 Fails to intersect lines				
60	41–42	CUTTING LINE *(Sitting at a table)* Give child **paper with 5 × ¼ in. line** and **scissors**. Run your finger along line and say, "Cut on the line."	2 Cuts within ½ in. of line the entire length of line 1 Cuts in direction of line but more than ½ in. from line 0 Snips with scissors				
61 Start: 47–54 months	41–42	COPYING CROSS *(Sitting at a table)* Place **paper, marker,** and **card with cross** on table. Say, "Draw lines just like these that cross in the middle."	2 Draws intersecting lines that are within 20 degrees of perpendicular and lengths on each side of middle vary no more than ¼ in. 1 Draws intersecting lines that are more than 20 degrees from perpendicular and/or lengths on each side of middle vary more than ¼ in. 0 Fails to intersect lines				

Item #	Age in Months	Item NAME, *Position*, and Description	Score Criteria	Administration 1	2	3	4
62	41–42	DROPPING PELLETS *(Sitting at a table)* Place **bottle** and **10 food pellets** on table. Say, "Put the food in the bottle as fast as you can. Put only 1 in at a time."	2 Puts 10 pellets in bottle in 30 seconds or less 1 Puts 5–10 pellets in bottle in 31–60 seconds 0 Puts 4 or fewer pellets in bottle in 60 seconds				
63 Start: 55–62 months	41–42	TRACING LINE *(Sitting at a table)* Place **paper with 5 × ¼ in. line** on table with line in horizontal position. Run your finger along the line and say, "Draw on this line. Try to stay right on the line."	2 Deviates off line no more than 2 times and by no more than ½ in. 1 Deviates off line 3–4 times and by no more than ½ in. 0 Deviates off line more than 4 times				
64	49–50	COPYING SQUARE *(Sitting at a table)* Place **paper, marker,** and **card with square** on table. Say, "Draw a square."	2 Draws lines that are straight and within 15 degrees of vertical and horizontal, with closed corners 1 Draws lines that deviate from vertical or horizontal by 16–30 degrees or a corner is open 0 Draws lines that deviate from vertical or horizontal by more than 30 degrees or 2 corners are open				
65	49–50	CUTTING CIRCLE *(Sitting at a table)* Give child **paper with circle on it** and **scissors**. Run your finger around circle and say, "Cut out the circle along the line."	2 Cuts within ¼ in. of line for ¾ of circle 1 Cuts within ½–¼ in. of line for ¼–¾ of circle 0 Cuts out circle more than ½ in. from line				
66 Start: 63–71 months	51–52	BUILDING STEPS *(Sitting at a table)* Build steps as pictured in Guide to Item Administration (**3 cubes** on bottom). Leave steps standing briefly. Then knock down and give **6 cubes** to child. Say, "Build the steps like I did."	2 Builds steps as illustrated 1 Builds steps with space between cubes or without proper alignment 0 Builds structure other than steps				
67	53–54	CONNECTING DOTS *(Sitting at a table)* Place **paper with 2 dots** and **marker** on table. Point to dots and say, "Draw a straight line from 1 dot to the other dot."	2 Connects dots; line does not deviate more than ¼ in. from horizontal 1 Connects dots; line deviates between ¼ and ½ in. from horizontal 0 Fails to connect dots or line deviates more than ½ in. from horizontal				
68	53–54	CUTTING SQUARE *(Sitting at a table)* Give **paper with square on it** and **scissors**. Run your finger around square and say, "Cut out the square along the lines."	2 Cuts out square within ¼ in. of lines 1 Cuts out square within ½–¼ in. of lines 0 Cuts out square more than ½ in. from lines				
69	53–54	BUILDING PYRAMID *(Sitting at a table)* **12 cubes** Build 6-cube pyramid as pictured in Guide to Item Administration and leave standing. Put **6 cubes** in front of child and say, "Build one like mine."	2 Builds pyramid as illustrated 1 Builds pyramid but cubes are touching in some places 0 Builds structure other than pyramid				
70	55–56	FOLDING PAPER *(Sitting at a table)* Show child **8.5 × 11 in. piece of paper folded in half lengthwise** and leave where child can see. Give child **piece of paper** and say, "Fold your paper to look like this one."	2 Folds paper in half with edges parallel and within ⅛ in. of each other 1 Folds paper in half with edges roughly parallel and within ½–⅛ in. of each other 0 Folds paper with edges more than ½ in. of each other				
71	59–60	COLORING BETWEEN LINES *(Sitting at a table)* Place **paper with parallel lines** and **marker** on table. Run your finger back and forth between lines and say, "Color only between the lines."	2 Colors ¾ of space without crossing lines more than 2 times 1 Colors ¾ of space and crosses line 3–4 times 0 Crosses lines more than 4 times				

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72	68–72	FOLDING PAPER *(Sitting at a table)* Show child **8.5 × 11 in. piece of paper folded in half twice** and leave where child can see it. Give child **piece of paper**. Say, "Fold your paper to look like this one."	2 Folds paper in half twice with edges parallel and within ⅛ in. of each other 1 Folds paper in half twice with edges parallel and within ½–⅛ in. of each other 0 Folds paper in half twice with edges more than ½ in. from each other				

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Clinical Approval	[redacted] I approve the document(s) 03-Sep-2023 13:43:53 GMT+0000

Clinical Approval	[redacted] I approve the document(s) 04-Sep-2023 09:49:42 GMT+0000

Statistics Approval	[redacted] I approve the document(s) 05-Sep-2023 12:08:55 GMT+0000

Signature Page for VV-CLIN-003803 v16.0