STATISTICAL ANALYSIS PLAN

PROTOCOL 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 Perdiatric Subjects

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1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Term
^{18}F-DOPA	L-6-[^{18}F] fluoro-3,4-dihydroxyphenylalanine
3-OMD	3-*O*-methyldopa
5-HIAA	5-hydroxyindoleacetic acid
AADC	Aromatic L-amino acid decarboxylase
AE	Adverse Events
AESI	Adverse Event of Special Interest
ATC	Anatomical, Therapeutic, and Chemical
Bayley-III	Bayley Scale Infant development, third edition
BLOD	Below limit of detection
BLOQ	Below limit of quantification
BMI	Body mass index
CRF	Case Report Forms
CS	Clinically Significant
CSF	Cerebrospinal Fluid
CTCAE	Common Terminology Criteria for Adverse Events
DDC	DOPA Decarboxylase (gene)
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
ECG	Electrocradiogram
ET	Early Termination
HVA	Homovanillic Acid
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MR	Magnetic resonance
MRI	Magnetic Resonance Imaging
NCS	Non-clinically Significant
OGC	Oculogyric Crisis
PD	Pharmacodynamic
PDMS-2	Peabody Developmental Motor Scale, second edition
PET	Positron Emission Tomography
PT	Preferred Term
QTcB	Bazett corrected QT measurement
QTcF	Fridericia corrected QT measurement
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Events
TEAESI	Treatment Emergent Adverse Event of Special Interest
TESAE	Treatment Emergent Serious Adverse Events
vg	Vector genome
WHO	Worl Health Organization

2. INTRODUCTION AND OVERVIEW

This Statistical Analysis Plan (SAP) is based on protocol of study PTC-AADC-GT-002 entitled, "An Open Label Trial to Address the Safety of the Smartflow ® MR-Compatible Ventricular Cannula for Administering Eladocagene Exuparvovec to Pediatric Subjects", V11.0. This SAP provides more details for the statistical analyses specified in the study protocol.

2.1. 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 Magnetic Resonance (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.

Subjects will return for regular visits during the course of the study. This study will have a Trial Phase, an Extension Phase, and a Long-Term Extension Phase. The length of the study, including the screening period, is 63 months (approximately 5 years).

The objectives of this study's Trial Phase, Extension Phase, and Long-Term Extension Phase are as follows:

- 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 Trial Phase will be completed 8 weeks after administration of eladocagene exuparvovec.
- The Extension Phase is designed to capture additional clinical information for eladocagene exuparvovec through study evaluations, including changes in motor development, AADC-specific symptoms, and other PD measures. The Extension Phase will be completed at 48 weeks after administration of eladocagene exuparvovec.
- The Long-term Extension Phase is designed to 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 formal review of safety data as outlined in the DSMB Charter. Review by DSMB will not be required to enroll successive subjects. The DSMB will monitor ongoing study results to ensure subject well-being, safety, and study integrity.

2.2. Study Objectives

2.2.1. Primary Objectives

The primary objectives are as follows:

- 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 MR-compatible ventricular cannula for administering eladocagene exuparvovec to pediatric subjects.

2.2.2. Secondary Objectives

The secondary study objectives are as follows:

- To assess the PD of eladocagene exuparvavoc by evaluating the following:
  - Homovanillic Acid (HVA) at Week 48
  - Positron emission tomography (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 exuparvavoc through Month 60 as assessed by the following:
  - Motor milestone attainment
  - Peabody Developmental Motor Scale, second edition (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 exuparvavoc treatment as assessed by treatment-emergent adverse events (TEAEs), neurological examinations, magnetic resonance imaging (MRI), and clinical laboratory tests.

2.3. Study Endpoints

2.3.1. Primary Endpoints

The primary efficacy endpoint is the change from baseline in HVA 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).

2.3.2. Secondary Endpoints

The secondary endpoints are as follows:

- Change from baseline in neurotransmitter cerebrospinal fluid (CSF) metabolites 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 cerebrospinal fluid (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.

2.4. Sample Size

The sample size is not based on statistical power consideration. A minimum of 3 subjects is planned to assess HVA levels at Week 8 and safety of the SmartFlow MR-compatible ventricular cannula for administering eladocagene exuparvovec to pediatric subjects.

3. ANALYSIS SETS

3.1. Pharmacodynamic 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.

3.2. Safety Population

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

3.3. 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.

Analyses of pharmacodynamic variables, safety and tolerability variables, and efficacy variables will be based on the pharmacodynamic population, safety population, and efficacy population, respectively.

4. GENERAL CONSIDERATIONS

Unless otherwise specified, continuous variables will be summarized by presenting the number of non-missing observations, mean, standard deviation, median, minimum, maximum, 25th percentile and 75th percentile.

Categorical variables will be summarized by presenting the number of subjects and percentage for each category.

All lab values that are reported as "< LLOQ" will be displayed in the listings as received but for summary statistics, this will be imputed as 0.5*LLOQ. For other laboratory values recorded as "< x.x" will be imputed as "x.x" minus 1 or other reasonable handling method as suggested by clinician for calculation.

When appropriate, study days will be listed in the data listings. For each subject, study day is measured relative to the day of study drug administration.

When data are summarized by visit, it will be based on nominal visit as shown on the case report form (CRF), and no date window will be applied. The site will be instructed to complete all assessments required for each study visit according to the schedule of assessments.

Analyses will be performed using SAS for Windows statistical software, version 9.4 or higher (SAS, Cary, NC), except where other software may be deemed more appropriate.

4.1. Estimand

The primary estimand is the change from baseline at Week 8 in HVA for subjects with AADC deficiency who meet the entry criteria for the study and received any amount of the study drug.

4.2. Interim Analysis

No interim analysis to decide whether to continue the study will be performed. However, for this open-label study, data summary may be performed while study is ongoing for Regulatory purpose.

4.3. Data Definition and Analysis Issues

The following derivations will be used in this study:

Baseline

The last non-missing data collected prior to drug administration is the study baseline.

Study Day

- For assessments done on or after date of study drug administration:

  Study day = Date of assessment – date of study drug administration + 1

- For assessments done before date of study drug administration:

  Study day = Date of assessment – date of study drug administration

Duration of follow-up

Duration of follow-up = last visit date recorded – date of study drug administration + 1

4.3.1. Handling of Dropouts or Missing Data

Missing data due to missed visits or withdrawal or death will not be imputed.

In administering PDMS-2, the following instructions were provided in the PDMS-2 Manual:

- **Entry Points:** The entry points are marked on each subtest in the Examiner Record Booklet. The entry points were determined empirically to allow the examiner to begin testing on an item that 75% of children in the normative sample at that age passed. When testing children with known disabilities, the examiner should use clinical judgement to determine the most appropriate entry point.
- **Basal Level:** The basal level is established when the child receives a score of 2 on 3 items in a row. The last three 2s before the 1 or 2 become the basal level. The examiner begins testing with the entry point item. If the child does not score 2 on each of the first 3 items administered, that is, if the child scores 0 or 1 on any of the first 3 items administered starting from the entry point, the examiner should test backward until the child scores 2 on 3 items in a row. This is the basal level. All items below the basal level are scored 2.
- **Ceiling Level:** Once the basal level has been established, the examiner administers progressively more difficult items until a ceiling is established. The ceiling is established when the child scores 0 on each of 3 items in a row. After the ceiling has been established, testing is discontinued. All items above the ceiling are scored 0.

If a score of 2 for items below basal level or score of 0 for items above ceiling are not entered in the evaluation, they will be filled in according to the instruction of the manual.

For each visit and subtest:

- An “observed” value is an item with a recorded value in a subtest (e.g., 0, 1, 2 and Not Evaluated).
- Within a subtest, all items prior to the first item with an “observed” score are considered “Basal” and are assigned the score of 2.
- An empty item in a subtest surrounded by “observed” values (e.g., there are “observed” values prior to the item and after the item), the value is to be left empty and considered “observed”.
- All items after the last recorded value in a subtest, or “observed” value (e.g., 0, 1, 2 and “Not Evaluated”), are considered “Ceiling” values and are assigned a score of 0).

The above will not affect summary and analyses of the study results because total scores collected in the case report form for each subtest are provided by the study site, and the study site included a score of 2 for all the basal items in the calculations of total score. The individual scores filled according to the manual as described above are only used to derive variables for motor milestone achievements.

For analysis and summary of motor milestones achievement, the following 3 terminologies will be used:

- Assessed: Item of interest is “observed” as defined above. This does not include score=0 assigned after reaching ceiling;

- Emerging: Item of interest has a Score =1;
- Mastery: Item of interest has a Score=2.

4.3.2. Adjustment for Covariates

When appropriate, baseline scores and age at the time of gene therapy will be used as covariates in the analysis model.

4.3.3. Multiple Comparisons and Multiplicity Adjustment

Not applicable.

4.4. Changes to Protocol Specified Analysis

No change.

5. SUBJECT DATA

5.1. Subject Disposition

A summary table for subject disposition will be provided for the number of subjects screened, number of screen failures, number dosed, number and percentage of subjects completed trial phase, extension phase, and long-term extension phase. Number of subjects and percentage of primary reason for discontinuation during each phase. Data listing for disposition information will be provided.

A summary table using descriptive statistics will be provided for duration of follow-up.

A separate listing for screen failure subjects will be provided.

5.2. Protocol Deviations

Protocol deviations will be recorded at the site in a deviation log separate from the clinical database. A data listing of all protocol deviations will be provided.

5.3. Demographic and Baseline Characteristics

A summary table will present descriptive statistics for age at onset, age at diagnosis, age at screening, age at gene therapy, height, weight, body mass index (BMI) and counts and percentages for sex, ethnicity, and race.

Listing for demographic characteristics including date of birth, age at onset, age at diagnosis, age at screening, age at gene therapy, date of treatment, sex, if female whether the subject is of childbearing potential, ethnicity, race, height, weight, and BMI will be provided.

Baseline assessments including genetic testing (method used in obtaining results, DDC gene variant allele 1 and DDC gene variant allele 2), CSF History (5-hydroxyindoleacetic acid, Homovanillic acid, 3-methoxy-4 hydroxyphenylglycol, Neopterin, Biopterin, 3-O-methyldopa, L-Dopa and 5-OH tryptophan), AADC Enzyme activity (Dopamine results, Dopamine range) will be presented.

A summary table of counts and percentages will be provided for genotype (homozygous and heterozygous).

5.4. Disease Characteristics

A summary of AADC-specific symptoms will be provided to show number and percentage of subjects with each symptom (floppiness, limb dystonia, stimulus-provoked dystonia, muscle tone, spontaneous movement, and muscle power), and the severity of symptom. A listing of AADC-specific symptoms will be provided.

5.5. Medical History

All medical conditions and surgical procedures will be classified by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) version 26.0 or most recent version.

The number and percent of subjects will be summarized for each SOC and PT. A subject will be counted only once for each SOC. A listing will be provided for medical history.

5.6. Prior and Concomitant Medications and Non-Drug Treatments

Prior and concomitant medications will be coded using World Health Organization (WHO) drug classifications version WHODrug B3 Global March 2023 or later.

The number and percentage of subjects will be summarized for each Anatomical, Therapeutic, and Chemical (ATC) level 3 term and PT. A subject will be counted only once for each ATC level term.

The reported name of drug or medication, ATC class, preferred name, indication, dose and units, frequency, route of administration, start date and end date, if not ongoing, will be listed.

5.7. Concomitant Procedure

All concomitant procedures will be classified by SOC and PT using MedDRA version 26.0 or later.

The number and percentage of subjects will be summarized for each SOC and PT. A subject will be counted only once for each SOC. The procedure, indication, and the procedure date will be listed.

5.8. Extent of Exposure

The total volume administered will be summarized using descriptive statistics. Counts and percentages will be provided for whether infusion was interrupted, and for the reason of interruption. Data collected for the study drug infusion record will be listed.

5.9. Intrasurgical MRI

A listing of intrasurgical MRI will be presented including the date it was performed, whether there was intracerebral hemorrhage, whether there was a leak during the study procedure, and the corresponding details if there is any.

5.10. Brain CT

Results (normal, clinically significantly abnormal and not clinically significantly abnormal) of brain CT performed pre-dose and post dose will be provided in a listing.

6. EFFICACY ANALYSIS

6.1. Primary Efficacy Analyses

The primary efficacy endpoint of observed values and change from baseline in HVA at Week 8 will be summarized using descriptive statistics. One-sample t-test will be performed for change and percentage changes from baseline to test whether the changes are statistically significantly different from 0.

6.2. Secondary Analysis

6.2.1. CSF Neurotransmitter Analysis

A summary table of descriptive statistics of the observed values, change from baseline and percentage change from baseline will be presented for 5-HIAA, HVA and 3-OMD by time point.

A listing for 5-HIAA, HVA and 3-OMD will be provided.

6.2.2. PET

The expression and activity of the AADC enzyme in the putamen will be assessed through PET imaging using ^{18}F-DOPA.

A summary table of descriptive statistics will be presented for the observed values and changes from baseline for the mean intensity, specific uptake, max standardized uptake and specific putaminal uptake. Percent change from baseline will be summarized for MAX specific putaminal uptake and specific putaminal uptake. One-sample t-test will be performed for change from baseline for variables in specific putaminal uptake to test whether change and percent change from baseline are statistically significantly different from 0.

A listing of the visual assessment of striatal FDOPA uptake, visual status, visual comments as well as general comments for caudate, putamen and occipital cortex will be provided. Also, mean intensity, specific uptake, max standardized uptake values, and specific uptake values will be presented for putamen and caudate.

6.2.3. Motor Milestones

Motor skills and development milestones will be assessed using PDMS-2. The PDMS-2 instrument will be administered by a qualified physiotherapist. Each skill item is assessed as a simple, 3-level scoring 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

Motor milestones are achieved in sequential order. Besides the key milestones listed in the protocol, intermittent milestones and more advanced milestones will be assessed. Each motor milestone based on individual item of PDMS-2 are displayed in Table 2. If subjects achieved more advanced milestones than listed, those milestones will also be summarized.

Table 2: Motor Milestones

Normal Age of Achievement	Analytical Term	PDMS-2 Reference (Position and subcategory)	PDMS-2 Description
3 months	Partial head control	Stationary 5	Aligning head (grasp child's hands and pull up to a sitting position, observe head alignment and position at end of cycle)
6 months	Full head control	Stationary 10	Aligning head (sitting, supported with pillows around hips)
6 months	Sitting with assistance	Stationary 11	Sitting (maintain for 8 seconds for score of "2")
10-11 months	Sitting unassisted	Stationary 14	Sitting (unsupported)
10 months	Standing with support	Locomotion 28	Stepping (supported)
11 months	Standing away from support	Locomotion 31	Standing (unsupported)
12 months	Walking with assistance	Locomotion 34	Walking (supported)
12 months	Walking to a toy	Locomotion 35	Walking (unsupported)
15-16 months	Walking up stairs with support	Locomotion 40	Walking up stairs (standing, facing flight of stairs, close to railing or wall)
17-18 months	Walking backward using normal stride	Locomotion 44	Walking backward
21-22 months	Walking on a taped line	Locomotion 48	Walking line

In assessing motor milestones achievement, if the PDMS-2 score for the question used to define a milestone achievement is 1, the milestone is considered "Emerging"; if the score for that question is 2, the milestone achievement is considered "Mastery". In the summary table, stages of milestone achievement used are:

- Emerging (PDMS-2 score =1 for the item assessed)
- Emerging and Mastery (PDMS-2 score=1 or 2 for the item assessed)
- Mastery (PDMS-2 score=2 for the item assessed).

The cumulative number of subjects achieving each motor milestone will be presented for each stage of achievement by timepoint after gene therapy. The number and percentage of subjects achieved each motor milestone for each stage of achievement by time point will be presented. In addition, new milestones observed at a visit that had not been achieved in prior visits for a subject will also be summarized.

Figure will be provided for cumulative milestones achievement by time point. Motor milestones achieved will be listed.

6.2.4. Fine Motor Grasping

Fine motor grasping score is also added as a secondary efficacy variable. Fine motor grasping score is calculated using the total score of the following 6 items from the Grasping section of PDMS-2:

- Item 7: Grasping rattle
- Item 14: Grasping cube
- Item 15: Grasping pellets using raking motion
- Item 16: Manipulating paper
- Item 17: Grasping pellets using thumbs and side of index fingers
- Item 18: Grasping pellets using pad of thumb and pad of index fingers

Summary statistics will be presented for observed score and change from baseline for each item and the total grasping score. Number and percentage of subjects achieved Emerging, Emerging and Mastery, and Mastery for each fine motor grasping item defined above will be summarized by timepoint.

6.2.5. Peabody Developmental Motor Scale, Second Edition (PDMS-2)

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. Therefore, no transformation will be performed.

A summary table of descriptive statistics will be presented for the observed scores and change from baseline for each subscale total score and the overall total score by visit.

PDMS-2 raw scores will be presented in a listing for the total score of each subscale performed and the overall total PDMS-2 score.

6.2.6. Bayley-III Assessment

Since Motor Scale has a lot of overlap with PDMS2, only the Cognitive and Language scales from the Bayley-III are used in this study. For convenience, the total of Cognitive and Language scores will be called Total Bayley score.

A summary table of descriptive statistics will be presented for the observed and change from baseline of the total score of Cognitive, Receptive, Expressive, Total Language (sum of Receptive and Expressive), and Total Bayley scores.

A listing of the Bayley-III assessments will be provided.

6.2.7. EQ-5D-Y

The EQ-5D-Y is a comprehensible instrument suitable for evaluating children and adolescents. The EQ-5D-Y descriptive system comprises of the following 5 dimensions: mobility, looking after myself, doing usual activities, having pain or discomfort, feeling worried, sad, or unhappy. The proxy version of the questionnaire 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 for subjects under 4 years of age. If the subject turns 4 during the study, the caregiver will complete the EQ-5D-Y per protocol.

A summary table of descriptive statistics will be presented for the raw "best health rate" score as well as the change from baseline.

A shift table representing a change from baseline for post baseline will be presented for each of the 5 dimensions.

A listing of the responses to each of the 5 dimensions as well as the "best health rate" will be provided for each visit. Change from baseline will be provided for the "best health rate".

6.2.8. Body Weight

A summary table of descriptive statistics of the observed and change from baseline will be presented. A listing of the weight observed and change from baseline will be provided.

6.2.9. AADC-Specific Symptoms

The count and percentage of subjects with each symptom will be presented by severity for floppiness, limb dystonia, stimulus-provoked dystonia, muscle tone, spontaneous movement, and muscle power by visit. A listing of AADC-specific symptoms severity and description including floppiness, limb dystonia, stimulus-provoked dystonia, muscle tone, spontaneous movement and muscle power will be provided.

6.2.10. Oculogyric Crisis

Episodes of oculogyric crisis (OGC) will be captured through paper or eDiary with specified questions.

Data from OGC diaries will be summarized in 2 ways:

1. Proportion of time and hours of OGC experienced per month
2. Frequency of OGC per month

The proportion of time for each subject will be calculated as total duration of all OGC episodes within the defined interval divided by total hours of that interval. Figures will be provided for the proportion of time and for the frequency of OGC per month.

If a subject did not have full month's record for a month at the beginning period prior to gene therapy or did not have full month's records for a month toward the end of the series of the

timepoints after gene therapy, the actual first date of reporting OGC in the diary (for prior treatment records) or the last date of reporting OGC in the diary (after treatment) for that month will be used to calculate total hours reporting OGC for that time period for that subject.

A listing of OGC data will be presented and will include start date and time, stop date and time, duration, medications taken, as well as pre-specified symptoms including uncontrolled eye movement, still limbs, lock jaw, neck dystonia, tongue thrust, trunk dystonia and overall assessment of severity.

6.2.11. Annual Rate of Respiratory Infection/Pneumonia

For pneumonia and respiratory infection, preferred terms under INFECTION and INFESTATION SOC selected for summary include the following:

- Bronchiolitis
- Bronchitis
- Pneumonia
- Pneumonia Haemophilus
- Pneumonia Influenzal
- Pneumonia Mycoplasmal
- Pneumonia Viral
- Respiratory tract infection
- Stenotrophomonas infection

Infections will be summarized as:

- Annual rate for all subjects after receiving gene therapy
- Annual rates prior to and after achieving head control (PDMS-2 score=2) for subjects who gained head control
- Annual rate after gene therapy for subjects who did not achieve head control.

Annual rate will be calculated using total time of all subjects in the study for that year as denominator and the total number of episodes of infection/pneumonia during that year as numerator:

Annual rate = (total number of episodes during that year)/(total time for that year)

7. SAFETY ANALYSES

7.1. Adverse Events

All AEs (serious and non-serious) occurring after completion of the informed consent process up to required reporting period, regardless of relationship to study drug, will be included and classified by SOC and PT using the MedDRA version 26.0.

7.1.1. Treatment-emergent Adverse Events

A TEAE is any AE that occurs post study drug administration. If onset date is missing, the AE is considered as TEAE.

An overall summary of TEAEs will be provided for number and percentage of subjects experiencing the following:

- TEAE.
- TEAE related to gene therapy.
- TEAE related to surgical device.
- TEAE related to neurosurgical procedure.
- TEAE related to F-DOPA.
- TEAE by severity.
- TEAE leading to withdrawal.
- TEAE of special interest (TEAESI: dyskinesia and cerebrospinal fluid leakage)
- Treatment emergent SAE (TESAE)
- TESAE and reasons for SAE
- TESAE related to gene therapy.

In the overall summary of TEAEs table, besides tabulating the number and percentage of subjects, the total number of TEAE episodes will also be provided. If a subject has repeated episodes of a particular TEAE, all episodes will be counted in the summary table.

Summary of number and percentage of subjects experiencing a TEAE will be presented for the following:

- TEAE by PT in descending order of incidence
- TEAE by SOC and PT
- TEAE related to gene therapy by SOC and PT.
- TEAE related to surgical device by SOC and PT.
- TEAE related to neurosurgical procedure by SOC and PT.
- TEAE related to F-DOPA by SOC and PT.
- TEAE by SOC, PT, and severity.

- TEAE leading to withdrawal by SOC and PT.
- TEAESI by SOC and PT.
- TESAE by SOC and PT
- TESAE related to gene therapy by SOC and PT

In the summary tables listed above, the percentage of subjects with TEAEs will be calculated by dividing the number of subjects who have experienced the event by the total number of subjects in the safety set. If a subject has repeated episodes of a particular TEAE, only the most severe episode, or the episode with the strongest causal relationship to study drug, will be counted in the summary tables.

A subject with more than one type of TEAE in a particular SOC will be counted only once in the total of subjects experiencing TEAEs in that particular SOC. Since a subject could have more than one type of TEAE within a particular SOC, the sum of subjects experiencing different TEAEs within the SOC could appear larger than the total number of subjects experiencing TEAEs in that SOC. Similarly, a subject who has experienced a TEAE in more than one SOC will be counted only once in the total number of subjects experiencing AEs in all SOCs.

In addition, a summary of dyskinesia will be presented to show number of subjects experienced treatment emergent dyskinesia, total number of events categorized by event severity, median time to first episode after gene therapy, and summary statistics of duration of dyskinesia.

All occurrences of all AEs will be listed for each subject.

7.2. Clinical Laboratory Tests

7.2.1. Chemistry

A summary table of descriptive statistics will be presented for the observed values and the change from baseline for chemistry parameters by time point. A listing of laboratory chemistry parameters will be provided.

7.2.2. Hematology

A summary table of descriptive statistics will be presented for the observed values and the change from baseline for hematology parameters by time point. A listing of laboratory hematology will be provided.

7.2.3. Coagulation

A summary table of descriptive statistics will be presented for the observed values and the change from baseline for activated partial thromboplastin, partial thromboplastin time, prothrombin time, and international normalized ratio by time point. Coagulation parameters will be listed.

7.2.4. Viral Shedding

Viral shedding results recorded as below limit of quantification (BLOQ) or below limit of detection (BLOD) will be classified as “Not Detected” and any positive value will be recorded as

"Detected". A shift table will be provided to display shift from baseline of "Detected" and "Not Detected" values. A listing of viral shedding results from blood, urine and CSF will be provided.

7.2.5. Anti-AAV2 Antibody

Number and percentage of subjects with positive and negative antibody (IgG) and neutralized antibody will be presented by visit. A summary table of descriptive statistics will be presented for the observed titer for IgG. A listing of anti-AAV2 antibody parameters will be provided by visit.

7.2.6. T-Cell

A summary table of number and percentage of subjects with positive, negative, and not suitable response will be presented by visit. A listing of T-Cell results will be presented by visit.

7.2.7. Brain MRI

A summary table of number and percentage of subjects with normal/abnormal results will be presented by visit.

A table for shift from baseline will also be provided.

A listing of Brian MRI results including the date performed, impression, overall results and if abnormal, the reason will be specified.

7.2.8. Chest X-Ray

A listing of chest X-Ray including overall X-Ray results (normal, CS abnormal and NCS abnormal) will be provided.

7.3. Vital Signs

A summary table of descriptive statistics will be presented for the observed values and change from baseline for weight, height, temperature, systolic blood pressure, diastolic blood pressure, heart rate, and respiratory rate. Vital sign data will be listed and will include weight, height, temperature, systolic blood pressure, diastolic blood pressure, heart rate, and respiratory rate.

7.4. ECG

The following corrections to the QT Interval (rounded by 1) will be computed and included in the summaries.

- *Bazett's correction:*

$$QTcB = \frac{QT}{RR^{1/2}}$$

- *Fridericia's correction:*

$$QTcF = \frac{QT}{RR^{1/3}}$$

Electrocardiogram interval measurements: heart rate, PR interval, RR interval, QRS interval, QT interval with Bazett's and Fridericia's correction, and overall interpretation (normal, clinically, and non-clinically significant abnormal or intermediate) will be provided.

7.5. Physical Examination

A listing of any complete physical examination, targeted physical examination including any abnormal findings and clinical significance will be provided.

8. MOCK TABLES, LISTINGS, AND GRAPHS

The study tables, listings and graphs shells will be provided in a separate document.