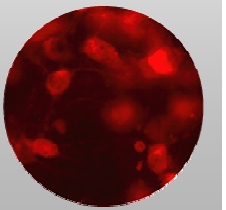
Parkinson's Disease

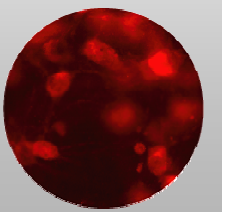
- Parkinson's Disease is the Second Most Common Neurodegenerative Disease After Alzheimer's Disease
  - Approximately 1 million patients in the USA
  - Mean age of onset is 60 years
- Cardinal Signs and Symptoms
  - Tremor, rigidity, bradykinesia, gait disturbance, postural instability
- Medical Therapies
  - Effective in early disease
  - Disability in advanced disease
    - Associated with motor complications
    - Do not affect all features (eg postural instability, dementia)
    - Do not slow disease progression
- Therapy That Restores Function And Slows Progression Is Major Unmet Medical Need



CERE-120 for Parkinson's Disease

Protocol: CERE-120-01

- A Phase 1, Open-Label Study of **CERE-120** [Adeno-Associated Virus (AAV2)-Neurturin (NTN)] to Assess the **Safety** and **Tolerability** of Intrastriatal Delivery to Subjects with Idiopathic **Parkinson's Disease**
- **RAC Protocol #: 0501-689**
- **Phase I Study Design**
  - Open-label
  - Dose-escalation
  - Two dose levels
  - 12 - 18 subjects total (6 – 9 / cohort)

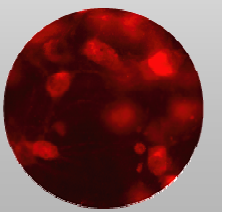


ceregene

CERE-120 for Parkinson's Disease

Objectives

- **Primary**
  - *Safety* and *tolerability* of two dose levels of CERE-120 in subjects with advanced idiopathic Parkinson's disease
- **Secondary**
  - UPDRS to assess anti-parkinsonian effects
  - ^{18}Fluorodopa PET imaging to assess nigrostriatal function



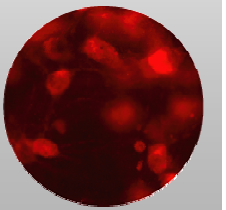
CERE-120 for Parkinson's Disease

Main Inclusion Criteria

- **Males** or **females** of any race aged 35 to 75 years old
- Advanced Parkinson's disease of at least 5 years duration
- Hoehn and Yahr stage 3 or worse when "off"
- Good response to levodopa in the judgment of the investigator
- Motor fluctuations not adequately controlled with medical therapy
- Stable doses of antiparkinsonian medications for 30 days prior to dosing

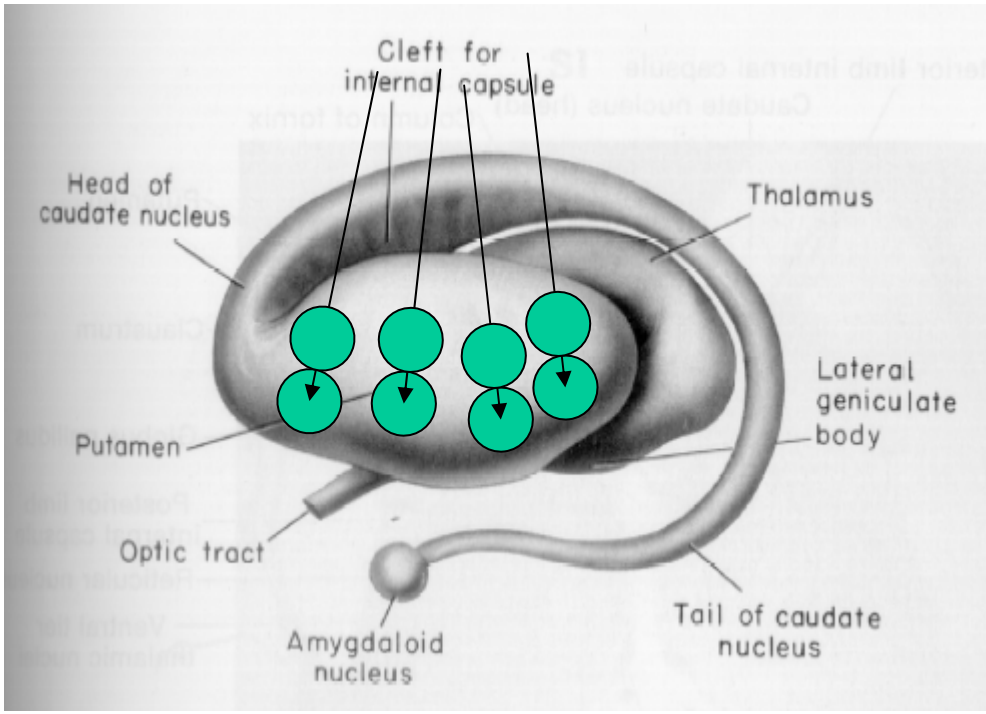
Main Exclusion Criteria

- Unable to give informed consent
- Atypical or secondary parkinsonism
- Clinically significant medical or psychiatric illness
- Previous intracranial neurosurgery or gene therapy



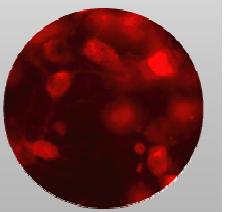
Dosing –Anterior and Posterior Putamen

- Estimated in-life putaminal diameter: 9-12 mm
- GOAL 1: Avoid ventricle/ependymal lining
- GOAL 2: Maximum coverage/minimum tracks



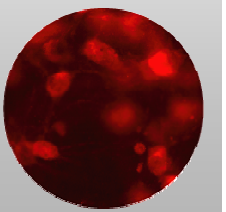
Importance of Putamen

- Major area of dopamine deficiency in PD
- Target of neurons that degenerate in PD
- Connects to primary and supplementary motor areas
- Distant from ventricles
- Easily targeted
- Significant neurosurgical experience
  - Transplantation procedures
  - Putamen for catheters infusing GDNF

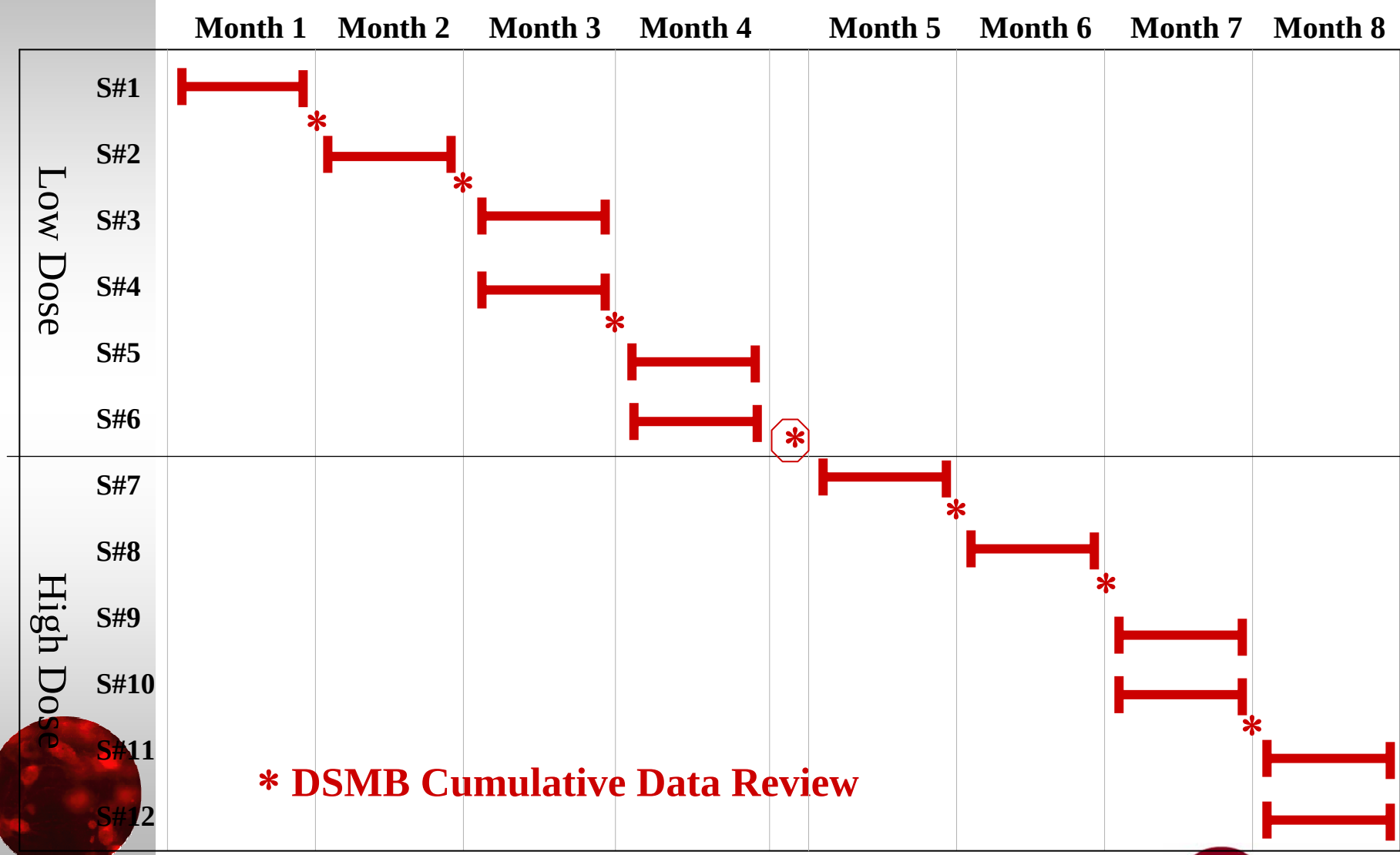


Why Not the Caudate?

- Less affected than putamen in PD
- Less connectivity to regions of SNc that degenerate
- Small dose of CERE-120 to caudate
- Necessitates reduced dose of CERE-120 to putamen
- Variable anatomy
- Adjacent to the lateral ventricle
  - Increases risk for accidentally depositing CERE-120 near or in the lateral ventricle
  - Adverse events from GDNF trials primarily linked to GDNF reaching non-target tissues via the CSF
  - Increased risk for neurological sequelae from accidental hemorrhage



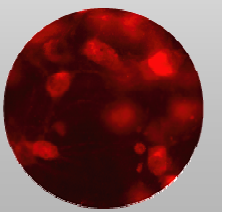
Schematic of Proposed Dosing Schedule for CERE-120



CERE-120 for Parkinson's Disease

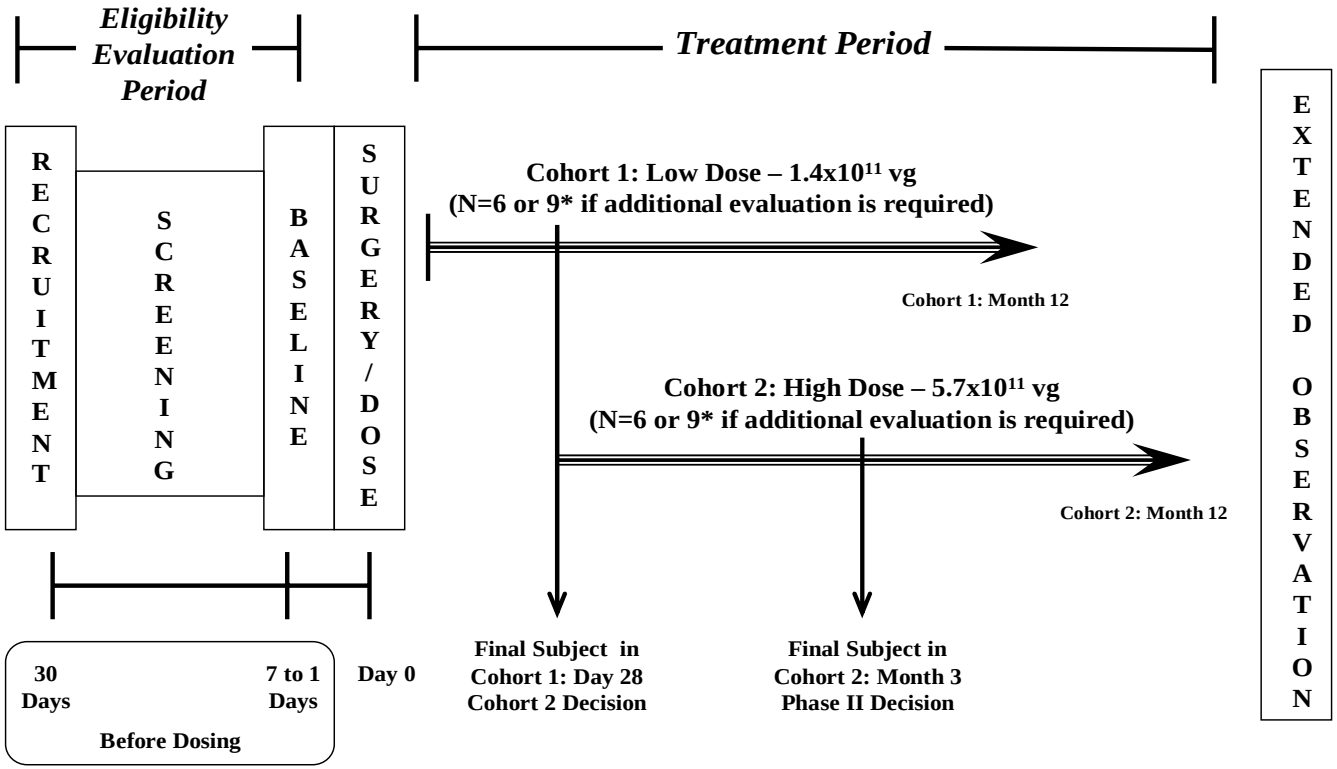
Enrollment Intervals

- Enrollment interval no less than every 28 days
  - Sequential enrollment of patients 1 and 2 at 28 day intervals
  - Concurrent enrollment of subjects 3 and 4 and subjects 5 and 6 at 28 day intervals
  - No less than 28 day interval between cohorts
  - Interval may be extended if additional evaluation is necessary
- Independent DSMB
  - The decision to proceed with enrollment of each subject or cohort of subjects will be made after consultation with the DSMB
  - Each decision will be made based on review of the cumulative clinical data obtained from the enrolled subjects



CERE-120 for Parkinson's Disease

CERE-120-01: STUDY DESIGN

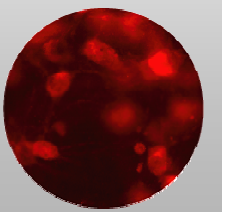


* For each cohort, the decision to include 3 additional subjects will be made at or before the cohort's sixth subject's Month 3 evaluations.

CERE-120 for Parkinson's Disease

Methodology and Procedures

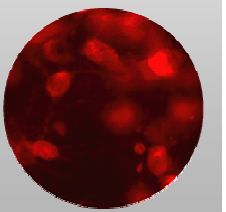
- **Assessment Times**
  - Evaluation Period (30 days before dosing)
    - Screening
    - Baseline (7 days before dosing)
  - Weekly study visits for first 28 days
  - Monthly study visits for first 3 months
  - Every 3 months thereafter for the first year
- **Safety Assessments**
  - Clinical and laboratory evaluations at every visit, serial MRIs
  - Ceregene will conduct continuous medical review during the course of the study
  - Data Safety Monitoring Board – Reviews data at each protocol-specified enrollment milestone (i.e., dosing and dose escalation)



CERE-120 for Parkinson's Disease

Assessments

- **Safety Assessments**
- **CERE-120 Antigenicity and Biodistribution**
  - Serum antibody response to AAV2 and NTN
  - Serum and urine levels of NTN and CERE-120
- **PD Efficacy Data**
  - Motor Function (UPDRS)
  - Motor Complications (Home diary)
  - Cognitive Function
  - Quality of Life
  - Investigator and subject-rated clinical global impression (CGI)
  - Striatal ^{18}F-dopa uptake with positron emission tomography (PET)



Criteria for Adding Patients to Cohort

- After review by the DSMB and the investigators a determination will be made regarding the necessity for additional patients
- Specific criteria that justify additional patients are:
  - Peri-operative complication that might preclude assessment of safety, tolerability and potential efficacy at 6 months
  - Intercurrent un-related medical illness that might preclude assessment of safety, tolerability and potential efficacy
  - WHO Grade 3 or 4 Toxicity in 1 of 6 patients