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)
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
  - \(^{18}\text{Fluorodopa PET imaging to assess nigrostriatal function}\)
CERE-110 for Alzheimer’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

CERE-120 for Parkinson’s Disease
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

Month 1 | Month 2 | Month 3 | Month 4 | Month 5 | Month 6 | Month 7 | Month 8
---|---|---|---|---|---|---|---
S#1 | S#2 | S#3 | S#4 | S#5 | S#6 | S#7 | S#8
Low Dose

S#9 | S#10 | S#11 | S#12 | S#7 | S#8 | S#9 | S#10
High Dose

* DSMB Cumulative Data Review
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-120-01: STUDY DESIGN

**Eligibility Evaluation Period**

<table>
<thead>
<tr>
<th>Recruitment Screen</th>
<th>Baseline Surgery/Dose</th>
<th>Treatment Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cohort 1: Low Dose – 1.4x10^{11} vg (N=6 or 9* if additional evaluation is required)</td>
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<td>Cohort 1: Month 12</td>
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<td></td>
<td>Cohort 2: High Dose – 5.7x10^{11} vg (N=6 or 9* if additional evaluation is required)</td>
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<td>Cohort 2: Month 12</td>
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</tbody>
</table>

30 Days

Before Dosing

7 to 1 Days

Day 0

Final Subject in Cohort 1: Day 28 Cohort 2 Decision

Final Subject in Cohort 2: Month 3 Phase II Decision

* 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.