A Phase I/II Trial Assessing the Safety and Efficacy of Bilateral Intraputaminal and Intranigral Administration of CERE-120 (Adeno-Associated Virus Serotype 2 [AAV2]-Neurturin [NTN]) in Subjects With Idiopathic Parkinson’s Disease
## Participants

<table>
<thead>
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<th>Title</th>
<th>Company</th>
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<tbody>
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<td>Institution</td>
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CERE-120: Innovative Therapy for PD

- **Adeno-associated virus** type-2 (AAV2) vector carrying gene for human **neurturin** (NTN)
  - Sole gene contained within AAV capsid is for therapeutic protein

- NTN is a naturally occurring potent growth factor for nigral dopaminergic neurons (an analog of GDNF)

- CERE-120 is administered by injection using standard stereotactic **neurosurgical procedure**

- Overcomes protein delivery issues by enabling local and persistent NTN protein expression within nigrostriatal system
Extensive CERE-120 Nonclinical Program

18 separate pharmacology, efficacy and safety/toxicology studies, establishing proof of concept, efficacy, safety and control of protein expression

- Compelling evidence of **efficacy** in range of rodent and monkey models relevant to PD
- **Control** of protein expression via orderly dose-response
- **No safety/toxicity** concerns, over range of excessive doses and times
  - No ‘maximum tolerated dose’ could be calculated

Seven peer-reviewed publications based on nonclinical program
Targeting Nigrostriatal Neurons With CERE-120

CERE-120 injected into terminal fields (putamen)

NTN expressed in putamen while vector and NTN protein transported to cell bodies in nigra (all animal studies)
CERE-120 Putaminal Injections Utilized in Phase 1 and Phase 2
CERE-120 Clinical Studies in PD

- **Phase 1** open label study (safety, tolerability, & potential efficacy)
  - Two sites (UCSF and Rush)
  - N=12 patients, dosing June/05 - March/06
  - Two dose levels (1.4 x 10^{11}vg and 5.4 x 10^{11}vg)
  - CERE-120 appeared safe; potential efficacy

- **Phase 2** randomized, double blind, sham surgery controlled study (efficacy and safety)
  - Nine leading movement disorder sites in USA; dosing Dec/06 – Oct/07
  - N=58, randomized 2:1 (CERE-120 : sham surgery)
  - One dose (5.4x10^{11}vg)
  - CERE-120 continued to appear safe; missed primary efficacy endpoint

- **Long Term follow up** of subjects from Phase 1 and 2 (ongoing)
  - Follow up 3-4 years (Phase 1) and 18+ months (Phase 2)
  - CERE-120 safety profile remains favorable
  - Sustained improvement in UPDRS Motor “off”
CERE-120 Safety Evaluation

- No significant change in clinical exam
- No clinically significant change in laboratory tests
- No CERE-120 detected in serum
- No antibodies to NTN detected in serum
- Modest increase in AAV2 antibody titer in a few subjects
  - No clinical manifestations observed
- Adverse event profile consistent with nature of surgical procedure
  - No serious adverse events deemed likely related to CERE-120
CERE-120 Phase 2 Study: Blinded Data Beyond 12 mos

- Of 58 subjects enrolled in the phase 2 study
  - 30 subjects completed a blinded assessment at 15 months
  - Of those, 14 also completed a blinded assessment at 18 months

- Opportunity to evaluate the longer-term effects of CERE-120 under controlled, blinded conditions
CERE-120 Phase 2 Synopsis

- Phase 2 study further supports the safety of both CERE-120 and the dosing procedures employed.

- **12 Months**: Primary efficacy endpoint showed no difference (change from baseline in UPDRS Motor “off”).
  - Several secondary endpoints suggest modest CERE-120 benefit.

- **18 Months**: Protocol-specified, blinded assessments of subjects (N=30) suggest a modest, but reliable improvement with CERE-120 on the primary measure (UPDRS motor off).

- No measure shows a similar advantage of sham over CERE-120 at any time point.
Brain Autopsy: Subset of NTN labeled sections

73 year old male: died of myocardial infarction 47 days post-op

- Quantitative analysis of all 3 brain hemispheres demonstrates a mean of 15% NTN coverage of the putamen
- No clear evidence of NTN in substantia nigra
Summary: NTN Expression in Advanced PD Brain

- CERE-120 performed as designed and intended:
  - clear NTN expression in and around injection sites
    - Volume of expression in putamen ~15%

- However, there was no clear evidence of NTN expression in the substantia nigra, in contrast to all nonclinical studies in rodents and nonhuman primates
NTN Signal in Monkey Nigra (positive) versus Human Nigra (negative)

Note clear NTN signal in monkey nigra, compared to non-specific staining on other 3 panels.
### Aged & MPTP Monkeys: NTN Coverage in Striatum Following CERE-120

<table>
<thead>
<tr>
<th>Monkey ID</th>
<th>NTN Volume CPu (mm³)</th>
<th>% Coverage CPu</th>
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<tbody>
<tr>
<td>0201</td>
<td>42.4</td>
<td>4</td>
</tr>
<tr>
<td>0202</td>
<td>190.3</td>
<td>19</td>
</tr>
<tr>
<td>0204</td>
<td>251.7</td>
<td>25</td>
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<table>
<thead>
<tr>
<th>Monkey ID</th>
<th>NTN Volume CPu (mm³)</th>
<th>% Coverage CPu</th>
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<tbody>
<tr>
<td>7177</td>
<td>77.33</td>
<td>8</td>
</tr>
<tr>
<td>7179</td>
<td>150.51</td>
<td>15</td>
</tr>
<tr>
<td>7181</td>
<td>82.86</td>
<td>8</td>
</tr>
<tr>
<td>7185</td>
<td>240.49</td>
<td>23</td>
</tr>
<tr>
<td>7193</td>
<td>134.95</td>
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 Mean: 14.4  
 Median: 14
NTN Expression in **Substantia Nigra**: Aged Monkeys

- **CERE-120 (signal)**
- **Uninjected (nonspecific)**

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<thead>
<tr>
<th>Monkey #</th>
<th>Striatal Coverage</th>
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<tbody>
<tr>
<td>0201</td>
<td>4%</td>
</tr>
<tr>
<td>0202</td>
<td>19%</td>
</tr>
<tr>
<td>0204</td>
<td>25%</td>
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NTN Staining in MPTP in Substantia Nigra: Monkey #7191 (15% Striatal Coverage)

Control Side

CERE-120 side

NTN staining in SN
NTN in Young Healthy Monkey: Low Dose CERE-120; 1.8% of Striatal Volume (@ 1 mo)

This section represents maximum NTN expression observed

Note clear exogenous NTN in nigra (due to retrograde transport from striatum)
CERE-120 Monkey High Dose Toxicity Study: Expression of NTN in SN

• Dose to striatum:
  • CERE-120: $5.1 \times 10^{12}$ (n=4) or $8.7 \times 10^{11}$ vg (n=4)
  • FB (n=4)
Summary: Primate NTN Expression In Striatum And Nigra

- Wide range of NTN coverage of striatum demonstrated by examples
  - 2 to 25% coverage easily bracket range of human PD autopsy cases
- As little as 2% NTN coverage sufficient to produce consistently clear NTN staining in nigra of young monkey
- In 15 other animal studies with CERE-120, similarly clear evidence of NTN transport to nigra seen

*Importantly, without NTN in nigra cell body, hard to fathom how CERE-120 could activate cellular repair genes or substantially improve DA function*
TH induction following CERE-120

- Tyrosine Hydroxylase (TH) is excellent marker for dopamine function and activity
  - Excellent marker for status of damaged dopamine neurons
  - Excellent marker for evidence of neurturin’s effects on repairing degenerating dopamine neurons
Relationship between NTN and TH in Aged Monkey Striatum

Note: intense TH signal (right panel) induced by NTN (left panel) with volume of TH exceeding that of NTN
NTN and TH in the Human Putamen
NTN and TH in the Human Putamen

Note: No TH induction seen in SN
Summary: TH Induction Following CERE-120 in Primates versus Humans

- All primate studies: marked increase in TH signal
- Human PD cases: no detectable TH induction in nigra cell bodies; very weak, sporadic TH signal noted in putamen
  - CERE-120 did not robustly improve dopaminergic neuron function or improve symptoms in PD
    - Explanation: induction of genes to repair cell and enhance DA synthesis requires adequate NTN protein in cell body
### Summary: Comparison of CERE-120 Bioactive Chain of Events

<table>
<thead>
<tr>
<th>CERE-120</th>
<th>Neurturin expression: STRIATUM</th>
<th>Neurturin expression: NIGRA</th>
<th>TH Induction: NIGRA</th>
<th>TH Induction: STRIATUM</th>
</tr>
</thead>
<tbody>
<tr>
<td>All monkeys (MPTP, aged and young)</td>
<td>+/-</td>
<td>+/-</td>
<td>++</td>
<td>++</td>
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<tr>
<td></td>
<td>+++</td>
<td>+++</td>
<td></td>
<td></td>
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<tr>
<td>Advanced PD Cases</td>
<td>++</td>
<td>(+)/--</td>
<td>-/?</td>
<td>(+)/--</td>
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CERE-120 Bioactivity: Simulation in Normal versus Parkinson’s Brain following Striatal Administration

Normal axonal transport

Impaired axonal transport

CERE-120 Injection

Striatum

Substantia Nigra

Neurturin

TH

NTN / CERE-120

TH

NTN / CERE-120
Implications of Data

- To maximize bioactive effects of CERE-120 in advanced PD, need to add ‘substantia nigra target’ to assure adequate NTN is expressed in cell body.

- Therefore, revised plan will both target nigra directly, as well as expand coverage of putamen.
Phase 1/2 Study (CERE-120-09)

Synopsis

A Phase I/II Trial Assessing the Safety and Efficacy of Bilateral Intraputaminal and Intranigral Administration of CERE-120 (Adeno-Associated Virus Serotype 2 [AAV2]-Neurturin [NTN]) in Subjects With Idiopathic Parkinson’s Disease
CERE-120 Phase 1/2 Study Design

- Phase 1 portion (N=6): open label (safety/feasibility)
  - First cohort (N=3)
    - SN dose of $4.0 \times 10^{11}$ vg
    - Putamen dose of $5.4 \times 10^{11}$ vg (same as in the Phase 2 study)
  - The second cohort (N=3)
    - SN dose of $4.0 \times 10^{11}$ vg
    - Putamen dose up to $2.2 \times 10^{12}$ vg (4x increase from Phase 2)

- Phase 2 portion (N~52): randomized (1:1), sham-surgery controlled
  - Primary endpoint: UDPRS Motor “off” at last blinded observation
    (minimum 15 months)
Phase 1/2 Inclusion Criteria

- Males and females ages 35 – 68 years old.
- The subject must have a diagnosis of bilateral, idiopathic PD based on UK Brain Bank criteria.
- Motor complications despite adequate antiparkinsonian therapy.
- A Hoehn and Yahr score no greater than 3 in the “off” condition
- A robust response to levodopa in the opinion of the investigator
- Stable dose of antiparkinsonian medications
Phase 1/2 Inclusion Criteria

- A score of 130 or greater on the Mattis Dementia Scale
- A score of 28 or less on the Beck Depression Inventory II
- The subject is medically fit to undergo neurosurgery
- The subject is physically and mentally capable of performing the necessary protocol-specified assessments
Phase 1/2 Exclusion Criteria

- Any subject for whom participation in the study would pose a safety risk, including but not limited to subjects with:
  - Compromised health status
  - A history of significant drug–induced hallucinations or neuroleptic treatment within the twelve months prior to Screening
  - History of schizophrenia, psychosis, major depression, alcohol abuse.
  - Serious medical illness, including significant cardiovascular risk
  - Any other condition that could lead to medical or neurological disability and therefore confound assessments during the course of the study (e.g., severe degenerative joint disease, arthritis, compromised nutritional state, neuropathy, morbid obesity, etc.)
  - Any clinical evidence of cognitive impairment
Phase 1/2 Exclusion Criteria (ctd.)

- Secondary parkinsonism
- Presence of any known brain abnormality that may interfere with the assessments of safety or efficacy or would, in the judgment of the investigator, represent a surgical risk to the subject.
- Evidence of significant brain atrophy per Baseline MRI.
- History of cancer within the past three years
- History of PD treatment by any procedure involving intracranial surgery or implantation of a device.
- Chemotherapy, immunotherapy, recent vaccinations
- History of prior gene transfer therapy.
- Treatment with an investigational agent within 90 days