

# Safety and Feasibility of Intranigral and Intraputaminal CERE-120 (AAV2-neurturin) administration in Parkinson's Disease

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## Abstract

### Objective:

To evaluate the feasibility and safety of CERE-120 administration to substantia nigra (SN) and putamen in Parkinson's disease (PD) in an open-label Phase-1 trial.

### Background:

CERE-120 employs gene transfer to deliver neurturin (NRTN), a neurotrophic factor that enhances dopaminergic neuron function and survival in animal models of PD. Intraputaminal CERE-120 in 50 PD patients followed postoperatively for 3-5 years appears safe. Whereas the completed double-blind, sham-surgery-controlled Phase-2a study failed to meet the primary-endpoint (UPDRS motor "off") at 12-months, the primary endpoint was reached for a subset of patients with double-blind assessments up to 18-months, as were several secondary endpoints, with no endpoint favoring sham-surgery (Marks et al., 2010, Lancet Neurology). Analysis of PD brain tissue post-CERE-120 in 3 patients showed that although NRTN is expressed in the putamen, minimal NRTN was transported to SN pars compacta, where it is required for induction of repair genes (e.g., Bartus et al., 2010, Mov Disorders). Following successful completion of nonclinical safety/feasibility tests, we are now testing CERE-120 delivered directly to the SN, combined with a higher dose to the putamen, to maximize the bioactivity.

### Methods:

Phase-1 open-label, two dose-cohorts (N=3, each). Both cohorts received 2.0x10<sup>11</sup> vector genomes (vg) into each SN; dose-cohort-1 also received into each putamen 2.7x10<sup>11</sup>vg (same as Phase-2a study) while dose-cohort-2 received 10x10<sup>11</sup>vg. Patients had idiopathic PD with robust response to levodopa but with motor-complications. The primary-endpoint was safety/tolerability.

### Results:

Each patient was dosed a month apart between 12/2009-6/2010. No surgical complications, serious adverse events or weight-loss occurred. Brain MRI at postoperative days 1 and 30 revealed no unexpected changes. Compared to baseline, UPDRS motor scores off medication improved an average of 22% at 9 months (N=6) and 19% at 12 months (N=3) (updated as of March, 2011)

### Interpretation:

Preliminary data supports safety and feasibility of intranigral and intraputaminal CERE-120 administration in this small study. A sham-surgery-controlled Phase-2b study is ongoing.

## Background and Objectives

- AAV2-NRTN (CERE-120), an AAV2 vector that delivers human NRTN, is being developed as a potential therapy for Parkinson's disease (PD) by Ceregene, Inc.
- NRTN, like GDNF, can protect nigrostriatal dopamine neurons from degeneration, restore function and thus has potential as a novel therapeutic for PD patients.
- Intraputaminal administration of CERE-120 in a Phase 1 (n=12) and a Phase 2a study (n=38) in advanced PD patients appears safe with follow up of 60+ months (Marks et al., 2008 and 2010).
- Modest benefits were seen in the completed Phase 2a study where 58 subjects were randomized to either receive CERE-120 or undergo a sham surgery procedure (Figure 1)

- Recent brain autopsy of PD patients treated with intraputaminal AAV2-NRTN (Bartus et al.) indicate that only limited amounts of NRTN are transported from the targeted striatum to the cell bodies in the SN, likely due to impaired axonal transport in PD.
- Before pursuing dual intranigral and intraputaminal dosing in the clinic, a series of nonclinical experiments were conducted to test the safety of NRTN expression in and around the SN (Tables 1 and 2) as well as potential efficacy (Figure 2) using a 200-fold dose range of CERE-120.

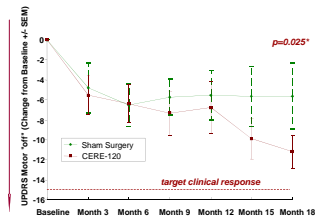


Figure 1. UPDRS Motor "off" score; change from baseline under double blind conditions

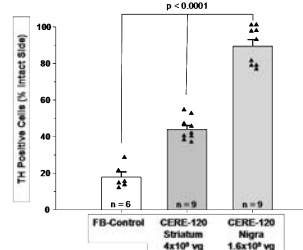
Group	# Rats	Injection Vol (µL)	Dosageform (vector genomes)	Designated Dose	Dose Description
Formalinn Solution	8	2 or 5	NA	FB	Control
AAV2-NRTN	8	2	0.32x10 <sup>10</sup>	Dose A	MSP dose projected to target SN
AAV2-NRTN	8	2	1.6x10 <sup>10</sup>	Dose B	Dose successfully projected to cover majority of SN
AAV2-NRTN	8	2	8x10 <sup>10</sup>	Dose C	SN higher dose than required to cover nigra
AAV2-NRTN	8	5	60x10 <sup>10</sup>	Dose D	~40X higher dose than required to cover nigra
AAV2-GDNF	8	2	8x10 <sup>10</sup>	GDNF	GDNF dose reported to increase body weight changes

Table 1: Dose response study targeting the SN with a range of AAV2-NRTN doses or formulation buffer (FB) in rats to test the safety and feasibility, as well as spread of protein

Figure 2: Nigral vs. striatal targeting of AAV-NRTN (CERE-120) to degenerating nigrostriatal dopamine neurons: Animals received AAV2-NRTN or FB control into either SN or striatum, simultaneously with an intrastratial injection of 6-OHDA. They were sacrificed 4 weeks later. Quantitation of TH+ cells in the SN revealed that nigral delivery of AAV2-NRTN resulted in far greater cell sparing (~90% of intact side), compared to striatal delivery (~44% of intact side) in a 6-OHDA paradigm of ongoing degeneration

MEASUREMENTS		OUTCOMES	
<b>In-life Safety and Tolerability</b>			
• Daily cap-sat-observations	• Weekly body weight	• No observable differences	• Modest reduction in wt gained, highest doses only
• Weekly food intake		• Modest reduction in locomotion	
<b>Neurobehavioral Examination</b>			
• Hind limb extension	• Cataleptic reflexes	• No apparent changes	• No change/difference
• Body temperature	• Open field behavior	• No change/difference	• No observable difference
<b>Transgene Expression</b>			
• NRTN mRNA throughout brain	• Quantification of NRTN distribution	• Dose-related spread of NRTN expression from targeted SN	• Dose-related increase in volume of NRTN expression
<b>Neurotoxicity</b>			
• NRTN staining throughout brain	• Histopathology, analysis (e.g. neuroinflammation, gliosis, cellular proliferation, hemorrhage)	• No evidence of inflammation, histological abnormalities or any other pathological change	

Table 2: Endpoints and safety results from dose-response study



## Methods

- Phase-1 open-label, two dose-cohorts (N=3, each)
- Both cohorts received CERE-120 2.0x10<sup>11</sup>vg into each SN
  - Dose-cohort-1 also received into each putamen 2.7x10<sup>11</sup>vg (same as Phase-2a study)
  - Dose-cohort-2 received 10x10<sup>11</sup>vg
- Eligibility
  - Between 35-70 y with idiopathic PD
  - Robust motor response to levodopa
  - Presence of motor complications (e.g. dyskinesia, wearing off, etc.)
  - No evidence of dementia or "extranigral" symptoms
- Primary-endpoint was safety/tolerability over 1 year

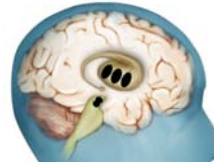


Figure 3. Expected NRTN expression following intraputaminal and intranigral stereotaxic CERE-120 delivery. Putamen: 3 needle passes with one drug deposit each and SN: 1 needle pass and two drug deposits

## Results

- Patients were dosed monthly between 12/2009-6/2010.
- Follow-up ranges from 9-12 months post-surgery
- No serious adverse events (SAEs) have been reported
- There were no surgical complications or prolonged hospitalizations
- All adverse events were mild/moderate and expected
  - Most were transient
- No weight loss
- Brain MRI at postoperative days 1 and 30, and at 1 year (N=3) revealed no complications
- Compared to baseline, UPDRS motor scores off medication improved an average of 22% at 9 months (N=6) and 19% at 12 months (N=3)

## Conclusions

- Preliminary data supports safety and feasibility of intranigral and intraputaminal CERE-120 administration in this small Phase 1 study
- Combined with nonclinical data showing safety at high dose multiples and an incremental benefit from dual administration (nigral + putamen) of CERE-120, Phase 1 data provide strong support for continued CERE-120 clinical development
- A randomized, sham-surgery-controlled, multicenter Phase-2b study in PD (N=52) is now underway at 11 centers across the US

## References

1. Marks et al., Lancet Neurology, 2008; vol. 7: 400-08
2. Marks et al., Lancet Neurology, 2010; vol. 9: 1164-72
3. Bartus et al., Movement Disorders, 2011 vol. 26, No.1: 27-36

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