AAV2-Neurturin (CERE-120) and Parkinson's Disease: The Safety and Feasibility of Combined Substantia Nigral and Putaminal Stereotactic Targeting Via a Phase 1/2b Clinical Trial in Advanced Parkinson's Disease

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Objective

To evaluate the safety and feasibility of AAV2-Neurturin (CERE-120) when administered bilaterally to the substantia nigra (SN) and putamen in subjects with idiopathic Parkinson's disease (PD).

Background

CERE-120 (AAV2-NRTN with the human NGF pre-pro sequence inserted) is designed to deliver the neurotrophic factor, neurturin (NRTN), to rejuvenate degenerating nigrostriatal neurons in moderately advanced ~~Parkinson's disease~~ (PD). A prior double-blind controlled Phase 2a trial supported the safety and established clinical proof of concept via significant benefit on several protocol-prescribed, blinded motor and QOL endpoints at 12 and 18 months. Although no measure favored the sham control, the trial failed to meet the primary endpoint (UPDRS motor-off at 12 months). Autopsy tissue from two treated subjects who later died of unrelated causes 1.5 and 3 months following CERE-120 demonstrated that CERE-120 produces targeted expression of NRTN and is also able to induce clear but ~~modest~~ enhancement of degenerating neurons in PD brains. ~~This analysis also revealed that neurons suffer serious~~ deficits in retrograde transport, impeding the transport of NRTN from the targeted putamen to the SN, ~~thus limiting~~ exposure to repair genes located in the degenerating cell bodies *(Bartus et al Mov Dis 2011).* This insight suggested that achieving maximum benefit from neurotrophic factors in PD likely requires targeting both the degenerating cell bodies in the SN and their terminal fields in the putamen.

Design / Method

A Phase 1/2b protocol was developed, targeting the **SUBSTANTIA NIGRA** directly, plus **increasing** the dose to the **PUTAMEN 4-fold** *(justified on the basis of additional clinical & nonclinical safety data)*

- **Formal risk: benefit evaluation** performed prior to initiating SN targeting~~, considering~~:
  - Feasibility of **stereotactic targeting** of SN~~, deep in the midbrain~~
  - ~~S~~afety of **exposing SN neurons** (and their afferents and efferents) to **AAV** and **NRTN**
  - ~~S~~afety of exposing ~~mistargeted~~ tissue in mid brain far removed from SN
- Also, several additional nonclinical studies conducted to further ~~potential~~ address safety issues *(Bartus et al Neurobio Disease, 2011)*
- **Phase 1b portion** (N=6): open label (safety / feasibility)
  - 3 centers in the US (*Duke, Mount Sinai, Emory*)
  - Surgeries conducted December 2009 – June 2010
  - 2 dose cohorts
    - First cohort (n=3): 9.4 x 10^{11} vg (total volume 140 µl)
    - Second cohort (n=3): 2.4 x 10^{12} vg (total volume 360 µl)
- **Phase 2 portion** (N=51): double-blind, randomized (1:1), sham-surgery controlled
  - 11 centers in the US
  - Enrollment completed in November 2011

DOSING PARAMETERS PER HEMISPHERE

A single burr hole was used, per hemisphere, permitting 3 separate needle tracts into each putamen and 1 into each nigra

PUTAMEN
1.0 x 10^{12} vg (150 µL)

SUBSTANTIA NIGRA
2.0 x 10^{11}vg (30 µL)

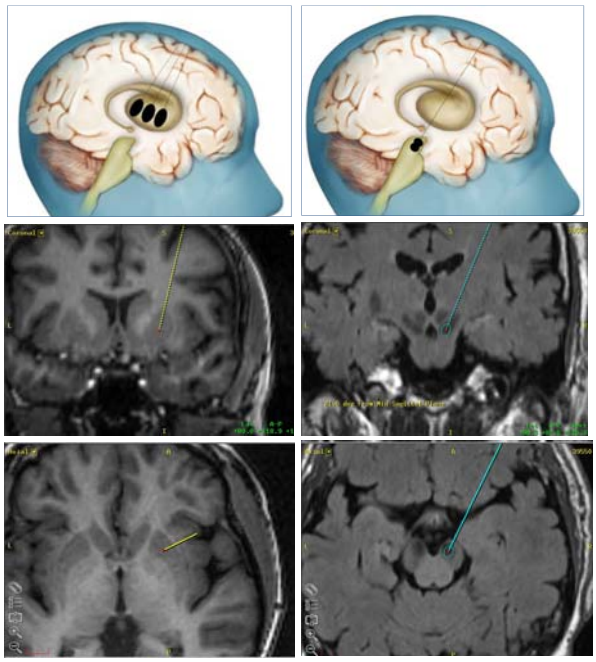

TABLE 1: PHASE 1b BASELINE CHARACTERISTICS OF PATIENTS

	Age (yrs)	Gender / Race	Length PD Dx (yrs)	H&Y stage, off/on	UPDRS III off/on
L1	45	M / White	6	3/1	34/7
L2	42	M / White	4	2.5/1	35/7
L3	48	M / White	11	3/2	35/14
H1	54	F / Black or African American	13	3/2	34/8
H2	63	F / White	7	3/2	50/8
H3	50	M / White	12	2/2	41/17
Mean (SD)	50.3 (7.5)	67% Male / 83% White	8.8 (3.7)	2.75 (0.4) / 1.67 (0.5)	38.2 (6.4) / 10.2 (4.3)

Patients are listed in the order in which they received treatment; M=male, F=female; L=low dose (9.4 x 10^{11} vg per patient); H=high dose (2.4 x 10^{12} vg per patient); H&Y=Hohn and Yahr disease stage; UPDRS III= Unified Parkinson's Disease Rating Scale, Motor Subscale

TABLE 2: PHASE 2b DEMOGRAPHICS (N=51)

Age (years)	
Mean (SD)	58.9 (6.4)
Median (Min, Max)	59 (46, 69)
Distribution of Age Categories	
35 to 50 years	7 (13.7%)
>50 to 65 years	36 (70.6%)
>65 to 70 years	8 (15.7%)
Gender	
Female	17 (33.3%)
Male	34 (66.7%)
Race	
White	49 (96.1%)
Black or African American	1 (2.0%)
Other	1 (2.0%)
Duration (Years) Since Diagnosis of Parkinson's Disease	
Mean (SD)	7.9 (3.3)
Median (Min, Max)	8.0 (3, 16)

Results

- As of June 2012
  - Over 24 months of safety data has been collected for all Phase 1b subjects
  - Over 6 months of safety data has been collected for all Phase 2b subjects
  - No SAEs have been reported in Phase 1 subjects
  - 12 SAEs have been reported in 9 Phase 2b subjects; all are inconsequential to the protocol, except two surgically-induced hemorrhages
    - First case was intraparenchymal hemorrhage in left thalamic/caudate area abutting the lateral ventricle
    - Second case was right frontal hemorrhage 15 days following surgical procedure
    - Both cases soon resolved and are asymptomatic
  - There have been no clinically significant alterations in physical or neurological ~~exam~~ findings, and no significant changes in vital signs, or clinical laboratory evaluations.
  - No weight loss (*Table 3)* or any other problems in medical status have been observed as a consequence of CERE-120 or the surgery
- An independent DMC routinely reviews unblinded safety data and has had no safety concerns related to the neurosurgical procedure, viral vector or NRTN expression.

TABLE 3: BODY MASS INDEX

		Mo. 0	Mo. 3	Mo. 6	Mo. 9	Mo. 12	Mo. 18	Mo. 24
PHASE 1b	L1	33.7	33.3	32.8	31.4	31.7	28.9	27.0
	L2	24.1	23.1	23.5	24.6	24.1	22.3	23.6
	L3	25.0	25.1	25.7	25.6	25.1	24.4	24.8
	H1	24.8	23.8	24.0	25.8	25.8	22.8	22.5
	H2	22.2	23.0	23.4	23.5	24.0	22.3	
	H3	20.5	20.2	20.3	20.8	20.3	20.5	
	Mean	25.1	24.8	25.0	25.3	25.2	23.5	
	SD	4.6	4.5	4.2	3.5	3.7	2.9	
PHASE 2b	Mean	28.2	28.6	28.7				
	SD	4.9	4.9	5.1				

BMI Reference:
- Underweight = <18.5
- Normal Weight = 18.5 – 24.9
- Overweight = 25 – 29.9
- Obesity = 30 or greater

TABLE 4: PHASE 1b RELEVANT ADVERSE EVENTS N=6

Incision Site Pain	4 (66.7%)
Dyskinesia	4 (66.7%)
Headache	2 (33.3%)
Abnormal Dreams	2 (33.3%)

TABLE 5: PHASE 2b RELEVANT ADVERSE EVENTS CERE-120 or Sham Surgery (N=51)

Headache	21 (41.2%)
Procedural Pain	11 (21.6%)
Nausea	8 (15.7%)
Dyskinesia	10 (19.6%)
Parkinsonism	6 (11.8%)

Table 4: Relevant adverse events reported in Phase 1b include those that occurred in more than a single patient.
Table 5: Relevant adverse events reported in Phase 2b include those that occurred in more than 10% of patients.

Summary and Conclusions

- Three clinical trials have been completed with CERE-120 (AAV2-NRTN) and a 4th pivotal trial has completed dosing and continues to evaluate subjects for efficacy and further safety.
- The first two trials targeted the putamen-only, whereas the last two trials targeted the putamen plus substantia nigra (SN) in order to compensate for evidence of impaired retrograde transport from the terminal field of the degenerating neurons (putamen) to the degenerating cell bodies (SN).
- Total duration of exposure from the initial two studies (Phase 1a and 2a) is 4.6 – 6.9 years (N=50 treated); duration of exposure to the current Phase 1b and 2b studies is 6 months – 2.4 years (N~30).
- Thus approximately 80 subjects across the entire CERE-120 program have over 280 cumulative patient-years exposure sustained NRTN expression, with no apparent safety issues
- The data reported in this poster (N= ~30 CERE-120 treated subjects) adds to the overall safety of CERE-120 by showing that combined bilateral targeting of the SN and putamen is feasible thus far appears safe, with over 35 cumulative patient-years exposure adding to the overall safety database

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