



The Development of CERE-120 (AAV-NTN) as a Novel Neurorestorative Therapy for PD: From Concept to Clinical Trials and Beyond

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Parkinson's disease: insidiously progressing, neurodegenerative disease

- Serious motor deficits: rigidity, bradykinesia, tremors
- While certain drugs effective for a finite period, they eventually become ineffective; patients suffer:
 - Significant “off” time (i.e., time with no therapeutic relief of symptoms, despite ‘optimal’ medication)
 - Significant “peak dose dyskinesias” (i.e., periods of debilitating, drug-induced, uncontrolled, violent movements)



An Urgent Need Exists For Improved Treatments For Parkinson' Disease

■ Treatments that

- **Improve function and vitality** of degenerating neurons
 - Reduce symptoms
 - Enhance existing medications
- Slow, halt, or **reverse neurodegeneration**
 - Slow disease progression
 - Protect remaining neurons

Neurotrophic Factors are naturally occurring proteins that can:

- **Repair** and **restore** function and vitality of damaged and dying neurons
- **Protect** neurons from further degeneration and death
- Presumably, **independent of etiology** and pathogenic variables
 - In animal studies, effective against any neural perturbation known
- Thus, they truly hold the **capacity to dramatically** improve treatments

Neurturin (NTN) and Parkinson's Disease

- Naturally-occurring neurotrophic factor
- In CNS, exerts neurotrophic effects on nigrostriatal dopamine neurons
- Loss of dopaminergic function (and cell death) strongly implicated as major source of motor impairments in PD
- Thus, NTN should improve motor symptoms and disease progression in PD
 - Independent of etiology or pathogenic variables

Editorial- Neurotrophic Factors: Can the Degenerating Brain Be Induced to Heal Itself?

“When one considers the history of neurology, the idea that one might be able to treat patients so that their brain cells might either withstand deadly perturbations or regenerate to a healthier, more functional state is truly revolutionary. Never before in the history of medical science could we imagine the means to induce damaged parts of the brain to heal.”

– *Bartus. R.T., Neurobiology of Aging, Vol. 10, p. 513, 1989.*

Human Trials Have Generally Failed to Translate Potential of Neurotrophic Factors

- Past 20+ years, numerous **human trials** produced **disappointing** results in ALS, AD, PD and others, independent of neurotrophic factor
- Nonetheless, animal biology, still likely predicts human therapy
- Rather, significant difficulty and complications involved with **delivery** have precluded successful clinical translation

Why Gene Transfer for Neurotrophic Factors?

Neurotrophic factors- robust complex proteins:

- Must be injected directly into brain; do not cross BBB
- Do not diffuse far from injected site
- Require continuous supply throughout targeted area
- Yield significant side effects when exposed to 'non-targeted areas'

Gene transfer: provides practical solution to all delivery problems, including sustained growth factor throughout targeted site

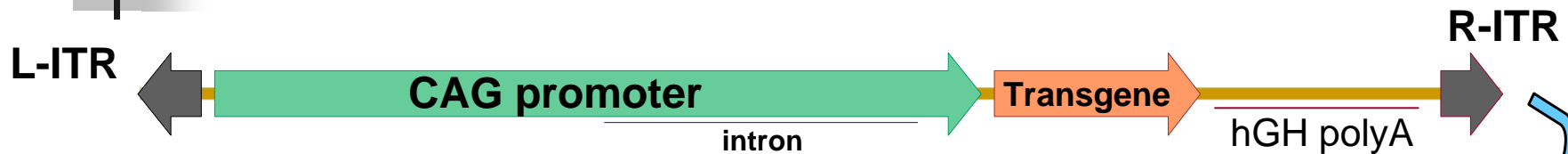
Ceregene believes gene transfer can...

...harness therapeutic powers of **neurotrophic factors** by solving obstacles of **safe and effective delivery**

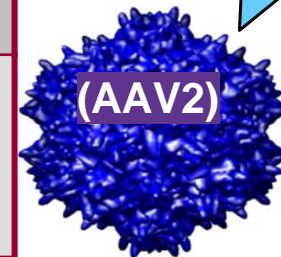
Key Characteristics of our Programs:

- Employ relatively safe **AAV vector**
- Administer relatively **small quantities** of vector **directly** to **targeted** brain site
- **Avoid significant systemic exposure** of vector and transgene
- Provide **permanent, stable** expression following single treatment

Ceregene's (AAV Vector) Product Pipeline

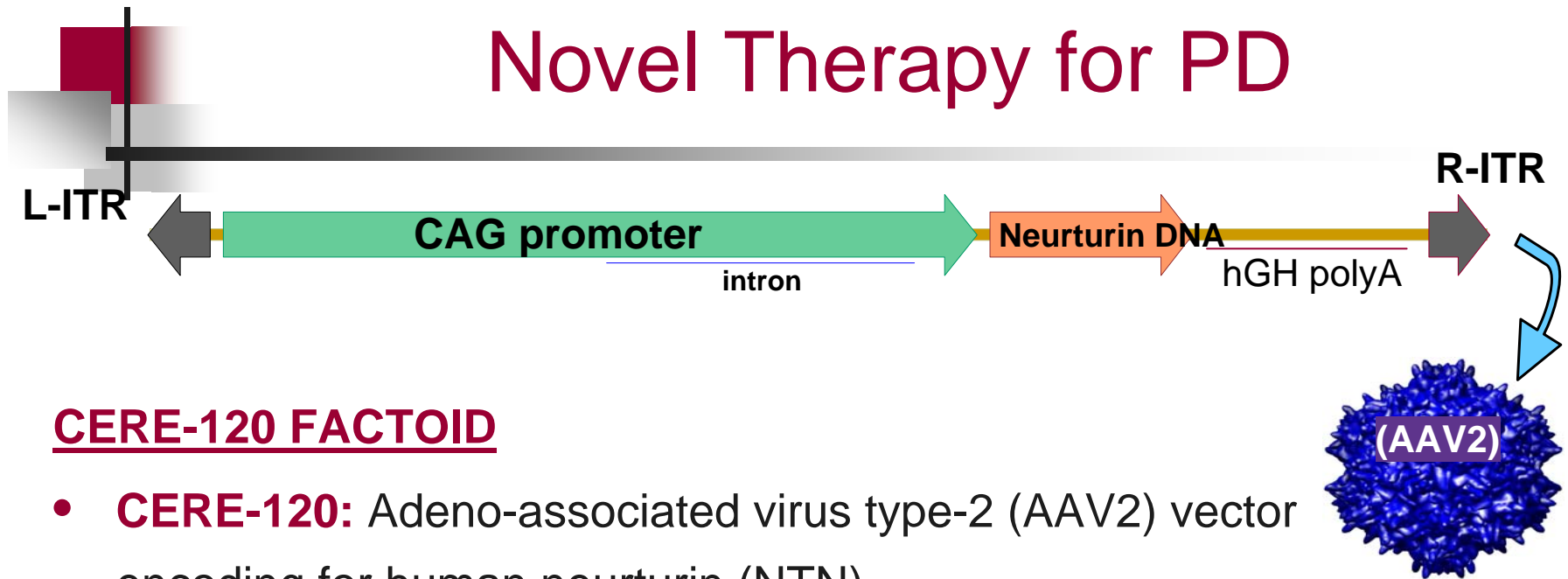


Product	Transgene	<u>Indication</u> ▪ status
CERE-120	Neurturin	<u>Parkinson's disease</u> ▪ Phase 1 completed ▪ Ph2 US completed ▪ EU Ph2: Q1-09
CERE-110	Nerve growth factor	<u>Alzheimer's disease</u> ▪ Initial Phase 1 completed ▪ Ph1 dose extension completed ▪ Controlled Ph2: Q1-09
CERE-140	NT4	<u>Retinitis Pigmentosa</u> ▪ Preclinical dev program <u>Age-related Macular Degen.</u> ▪ Preclin. Research Program
CERE-135	IGF1	<u>Amyotrophic Lat. Sclerosis</u> ▪ Preclinical Research Program



CERE-120 (AAV-NTN) for Parkinson's disease

CERE-120 as an Novel Therapy for PD



CERE-120 FACTOID

- **CERE-120:** Adeno-associated virus type-2 (AAV2) vector encoding for human neurturin (NTN)
 - Sole gene is therapeutic gene, contained within AAV capsid
- Provides effective means of delivering **persistent NTN** protein to **targeted** putamen in Parkinson's disease
- NTN (a naturally occurring analog of GDNF) is a potent neurotrophic factor for nigral DA neurons

Synopsis: CERE-120 Nonclinical Program

- **18 separate** pharmacology, efficacy and safety/tox **studies** conducted over 2 year period, establishing:
 - Extensive evidence of **efficacy** in range of rodent and monkey models relevant to PD
 - Excellent **control** of protein expression via orderly dose-response
 - extensive coverage of striatum, yet limited to target area
 - with no spread after 1 month
 - steady, continuous NTN expression confirmed beyond 1 year
 - Strong **safety/toxicity profile**, over range of excessive doses, up to 1 year in monkeys and rats



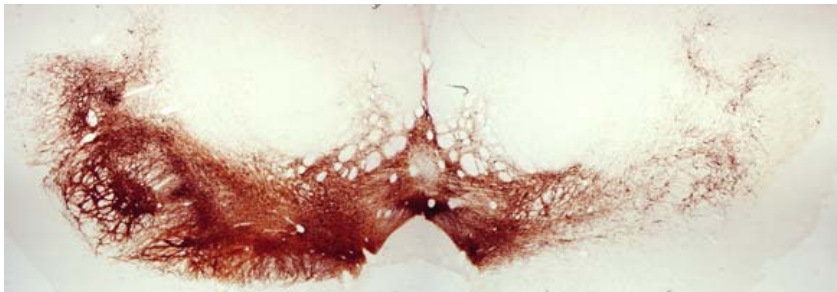
Does CERE-120 provide the desired trophic effect to nigral neurons

Multiple measures in multiple models: mutually corroborating evidence of CERE-120's efficacy

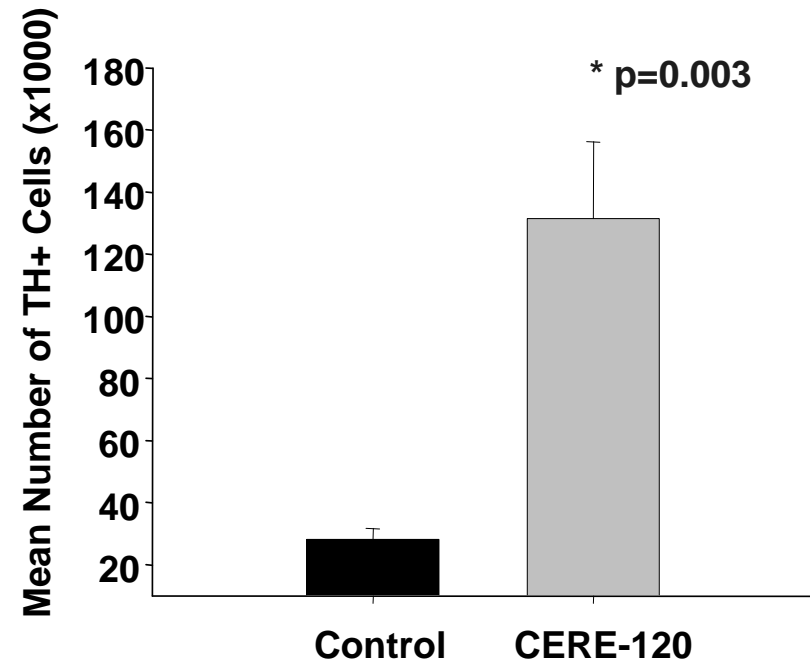
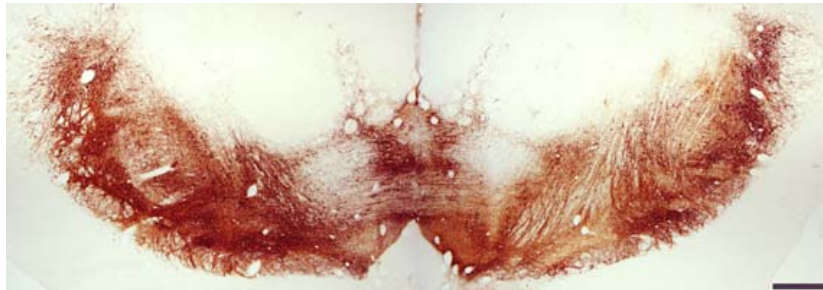
- **6-OHDA rat** model of PD (*Gasmi et al. 2007a; 2007b*)
 - Protection of nigral cells at multiple time points and range of doses
 - Functional (behavioral) benefit
- **Aged rats**
 - 'Classic' neurotrophic-induced hypertrophy of nigral neurons
- **Young, healthy monkeys** (Herzog et al, 2007a; 2007b)
 - Enhanced nigrostriatal TH & activation of pERK signaling
- **Aged monkeys** (Herzog et al, 2007c)
 - Enhanced ¹⁸F-Dopa PET uptake in striatum
 - Enhanced TH in striatum and TH and pERK in nigra
- **MPTP primate** model of PD (*Kordower et al, 2006*)
 - Long-lasting improvement in motor performance
 - Increased nigral neurons, TH in striatum, pERK activation

CERE-120 protects nigral TH neurons in MPTP monkeys

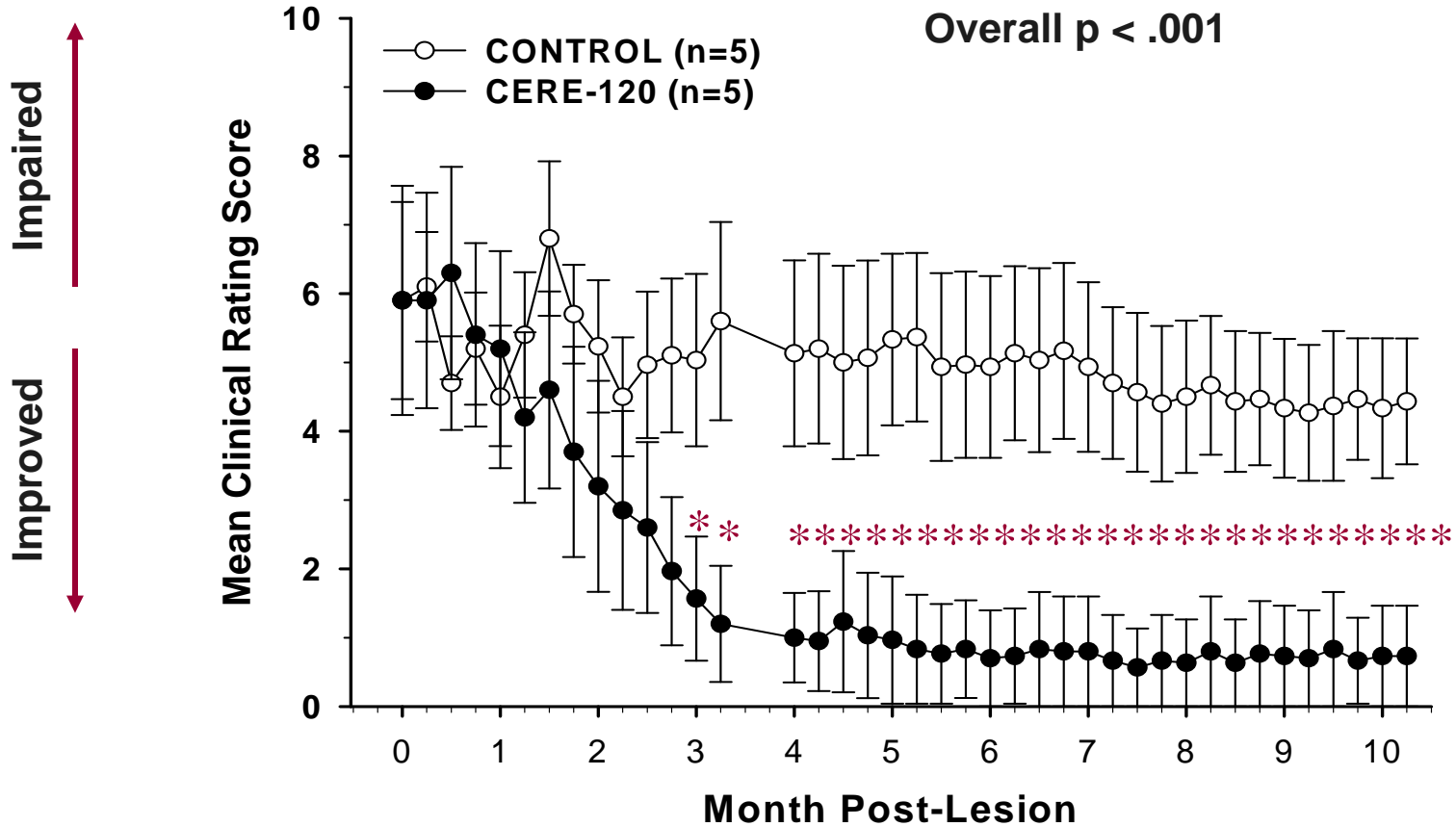
MPTP + Control



MPTP + CERE-120



MPTP Primate Model: CERE-120 improves motor performance persistently



*p < .05 to p < .001

Is CERE-120 Sufficiently “Well-Behaved” to Become a Product?

- **Is expression controlled and predictable?**
- **Is expression long-term and stable?**



Summary: CERE-120

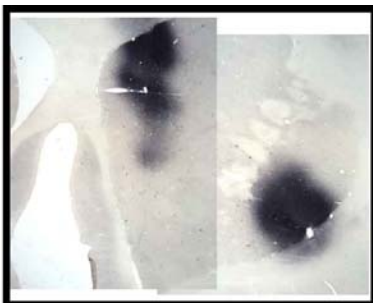
Kinetics of Expression

Orderly and Predictable Kinetics

- Volume of expression (morphometrics) and amount of protein (ELISA) both approach **asymptote** at approximately **4 weeks**
- Expression is **persistent and stable**, thereafter
 - 18 months in rats
 - 1 year in monkeys

Neurturin expression in primates can be controlled via dose of CERE-120

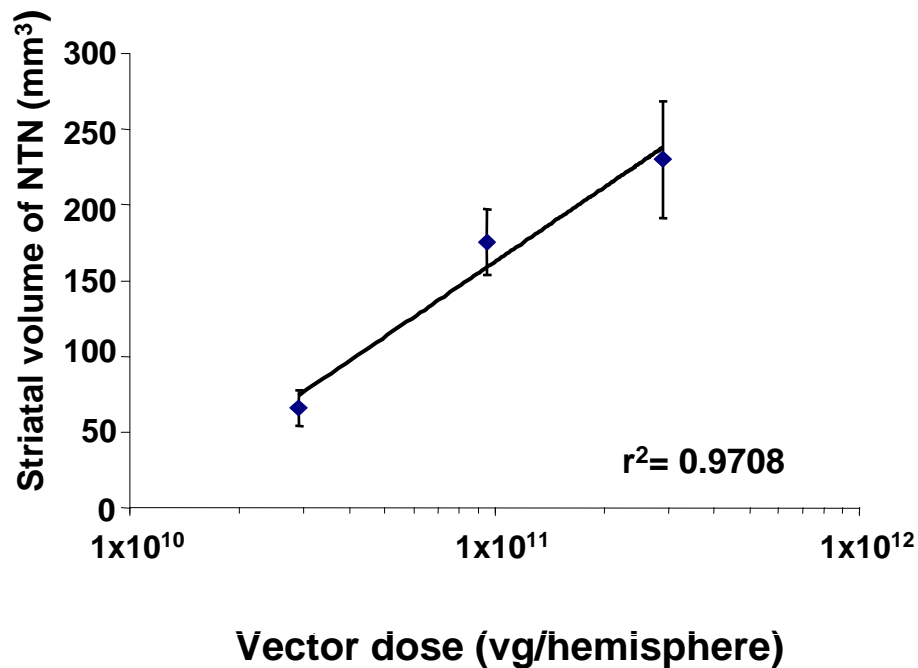
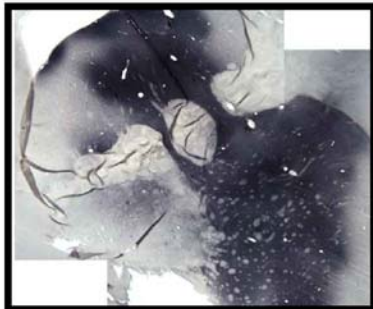
3×10^{10}
vg/hem.



1×10^{11}



3×10^{11}



Wide-spread coverage of NTN
achieved in targeted striatum



Will product be safe in humans?

'Pushed' dose to maximum level possible

- Dose multiples in rats (lowest efficacy to highest safety dose): 250 x
- Dose multiples from monkeys to humans: 100 and 400 x (by brain weight and volume)
- Found no evidence of toxicity in either rats or monkeys

Safety/tolerability profile in rats and monkeys: No toxicity detected

6 studies; Up to 12 months in both rats and monkeys

- No abnormalities in brain or **organ histopathology**
- No evidence of **brain inflammatory or immune reactions**
- No abnormalities on **neurological/behavioral exams**
- No **weight** loss
- No **Schwann cell hyperplasia**
- No evidence of **pain**
- No CERE-120 or NTN detected in **CSF**
- Virtually no systemic **immune response** to NTN
 - dose-related response to AAV2 but not associated with any other outcome



CERE-120 Safety Summary

- No evidence of toxicity or side effects on any measure, at any dose, at any time point in either rats or monkeys
- No ‘maximum tolerated dose’ could be calculated, even with excessive doses over long time points with persistent expression
 - Doses tested were hundreds of times greater than required for efficacy
 - Doses are hundreds of times higher (by brain weigh) than required for human subjects

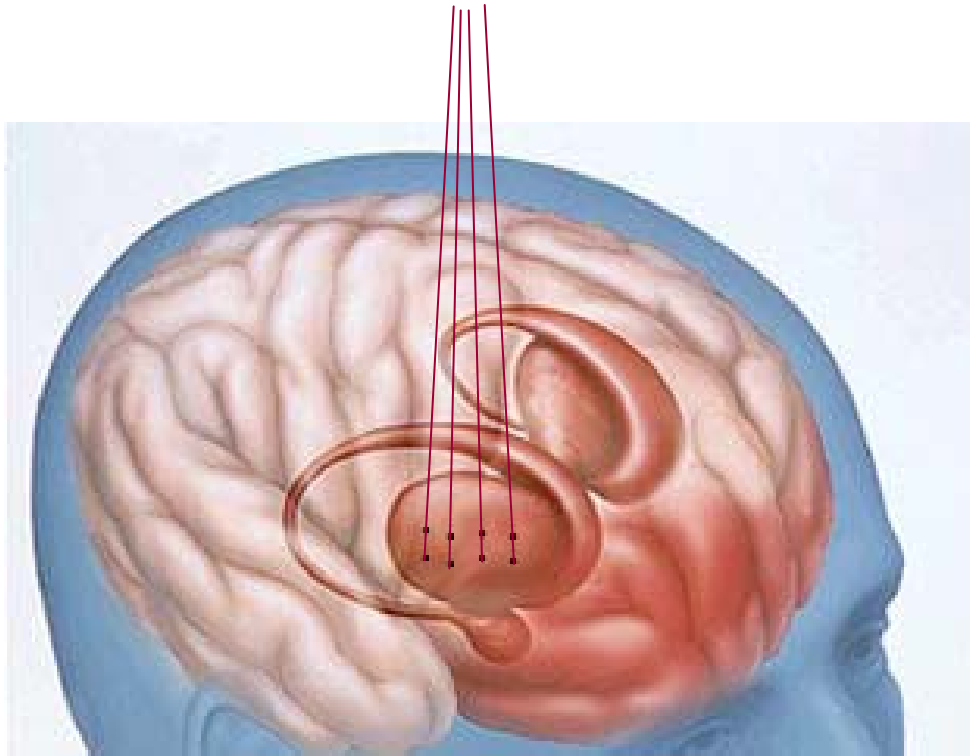


Update of clinical program

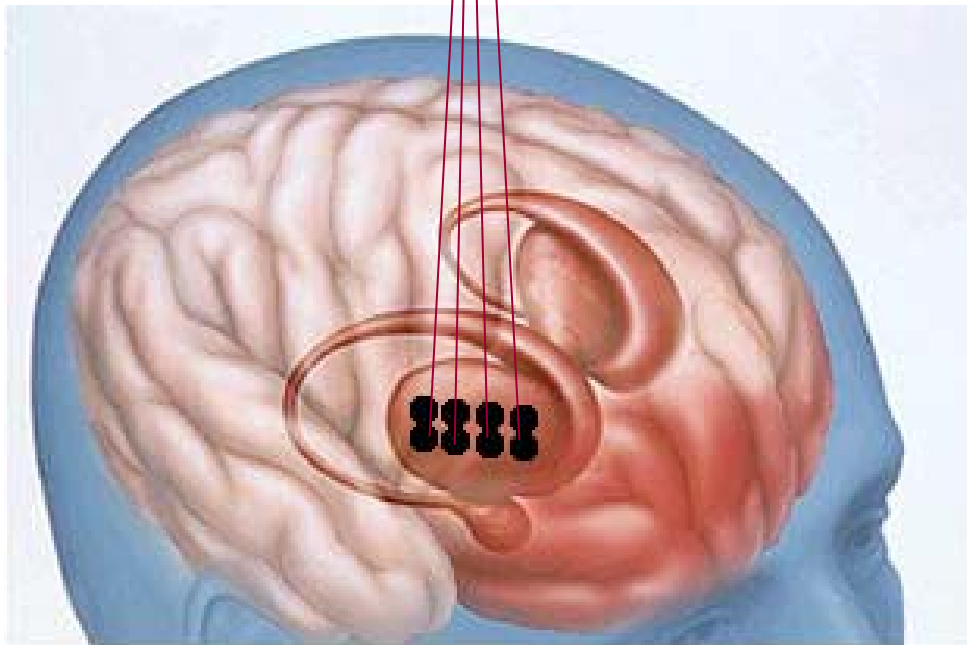
CERE-120 Clinical Overview

- Phase 1 open label trial (n=12) in USA
 - Completed
- Phase 2 double-blinded controlled trial (n=58) in USA
 - Completed; data by end of year
- Phase 2 trial in EU
 - To be launched- 1st Quarter '09 (with Genzyme)
- Long-term follow up for all patients dosed

Treatment Goal: Distribute growth factor throughout major areas of Putamen...



... While at same time, avoiding protein spread outside targeted Putamen...



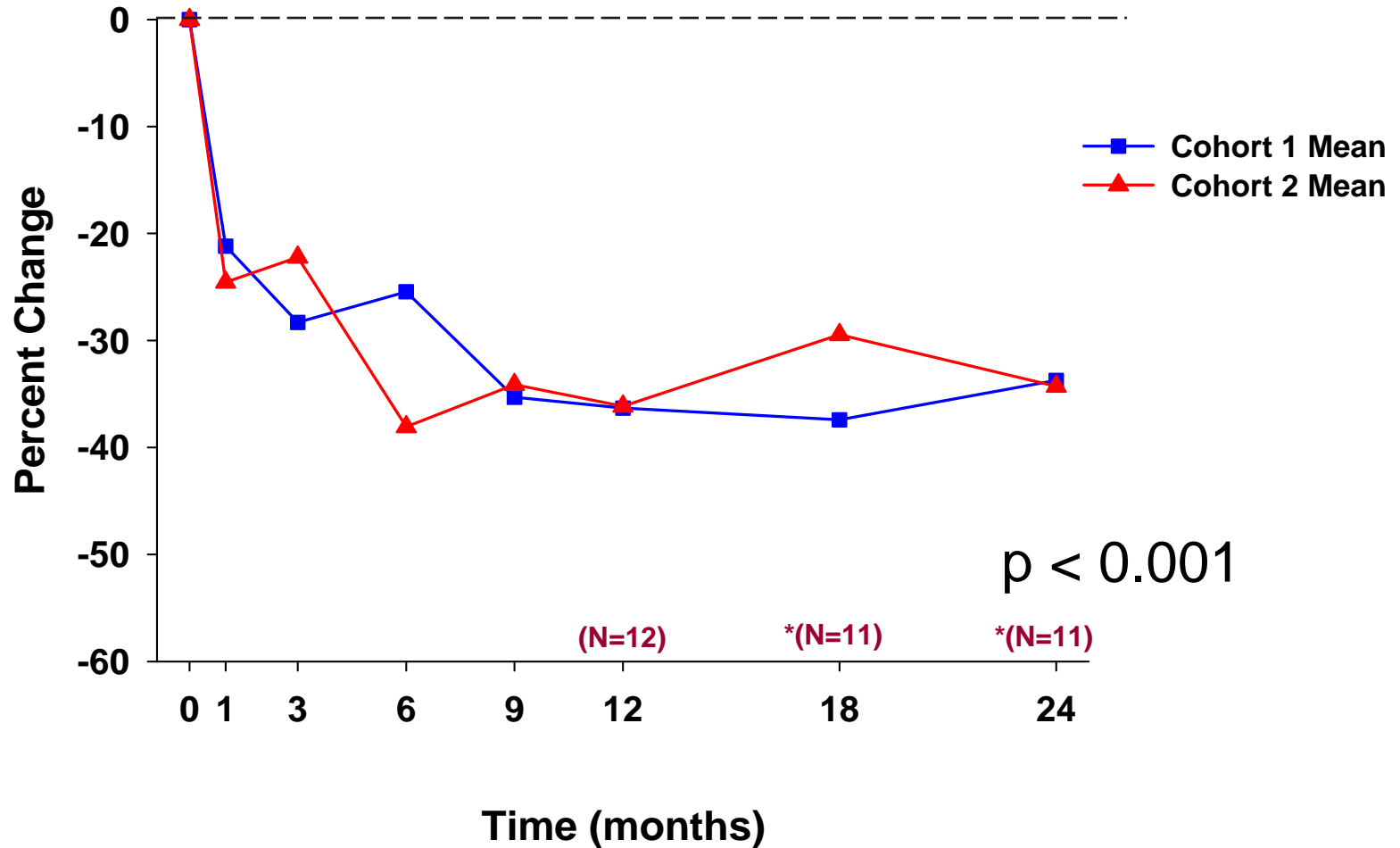
CERE-120 Phase 1 Study Design

- Purpose: investigate safety, tolerability, & potential efficacy of CERE-120 in **advanced Parkinson's patients**
- 12 patients: PD for 5+ years, significant off time with motor fluctuations
 - 6 subjects (4 UCSF, 2 Rush): low dose (1.3×10^{11} vg)
 - 6 subjects (4 UCSF, 2 Rush): high dose (5.4×10^{11} vg)
- Bilateral administration for all subjects
- Initial protocol: 12 month evaluation; subjects now enrolled in long term follow up protocol

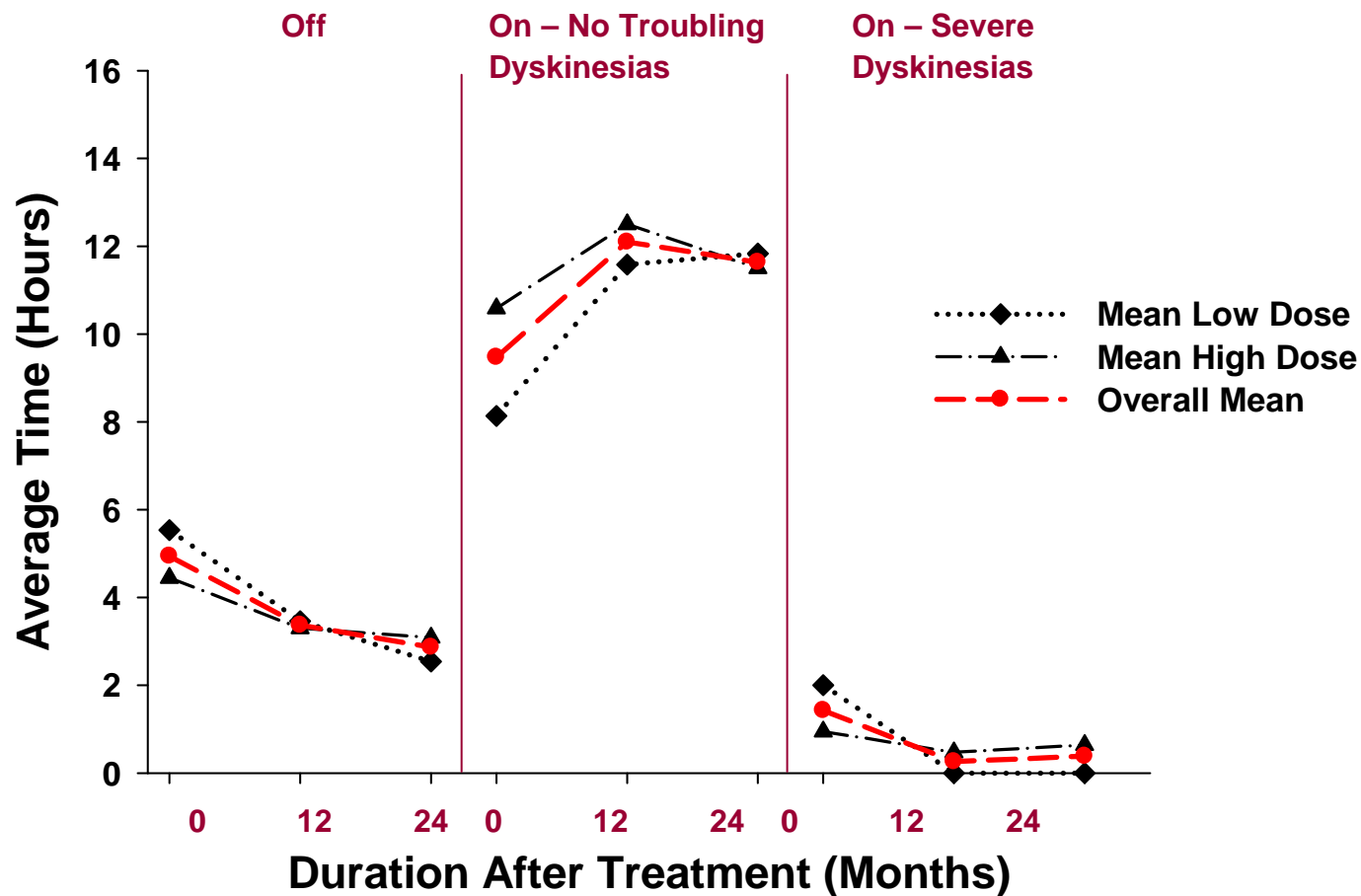
CERE-120 Phase 1 Results: Adverse Events

- No serious adverse events (SAEs) observed
- A variety of non-serious, ***transient*** adverse events noted

CERE-120 Long Term Follow Up: Change in UPDRS motor (%)



CERE-120 Long-term Follow Up: 3-day Patient Diaries (assessed when patient is on optimal medication)



Phase 1 Conclusions: CERE-120

- CERE-120 appears **safe and well-tolerated** in advanced PD subjects (no CERE-120 SAEs)
 - all subjects now 2+ yrs, post-dosing
- **Efficacy** measures all **tracking positively**, with increasing effects seen over several months and persisting for up to two years

Important Caveats: Phase 1 data

- Open label study; no blinded control
- Small number of patients
- Highly motivated investigators and patients
- Thus, all results are preliminary and conclusions tentative, at best
- Results require replication and extension in larger, well-controlled trial

CERE-120 Phase 2 Trial

- Multi-center, double-blind, controlled trial
- 58 subjects (2/3 treated; 1/3 sham surgery)
 - 5.4×10^{11} vg: higher of two doses in Phase 1
- Sham surgery: partial burr holes
 - Treatment offered after blind broken
- Nine Movement Disorder Centers participating
 - Open enrollment
- End-points parallel those of Phase 1 trial
 - With more emphasis on efficacy

CERE-120 Phase II Centers

<i>Institution</i>	<i>Neurologist</i>	<i>Neurosurgeon</i>
<i>UCSF, San Francisco, CA</i>	<i>William Marks</i>	<i>Phil Starr/Paul Larson</i>
<i>Cleveland Clinic</i>	<i>Jerome Vitek</i>	<i>Nick Boulis</i>
<i>Duke, Durham, NC</i>	<i>Mark Stacey</i>	<i>Dennis Turner</i>
<i>Rush, Chicago, IL</i>	<i>Leo Verhagen</i>	<i>Roy Bakay</i>
<i>UAB, Birmingham, AL</i>	<i>Ray Watts</i>	<i>Barton Guthrie</i>
<i>Mt. Sinai, New York, NY</i>	<i>Michele Tagliati</i>	<i>Ron Alterman</i>
<i>Baylor, Houston, TX</i>	<i>Joseph Jankovic</i>	<i>Richard Simpson</i>
<i>UPenn, Philadelphia, PA</i>	<i>Matthew Stern</i>	<i>Gordon Baltuch</i>
<i>OHSU, Portland, OR</i>	<i>John Nutt</i>	<i>Phil Starr/Paul Larson (UCSF)</i>



CERE-120 Controlled Phase 2 Trial

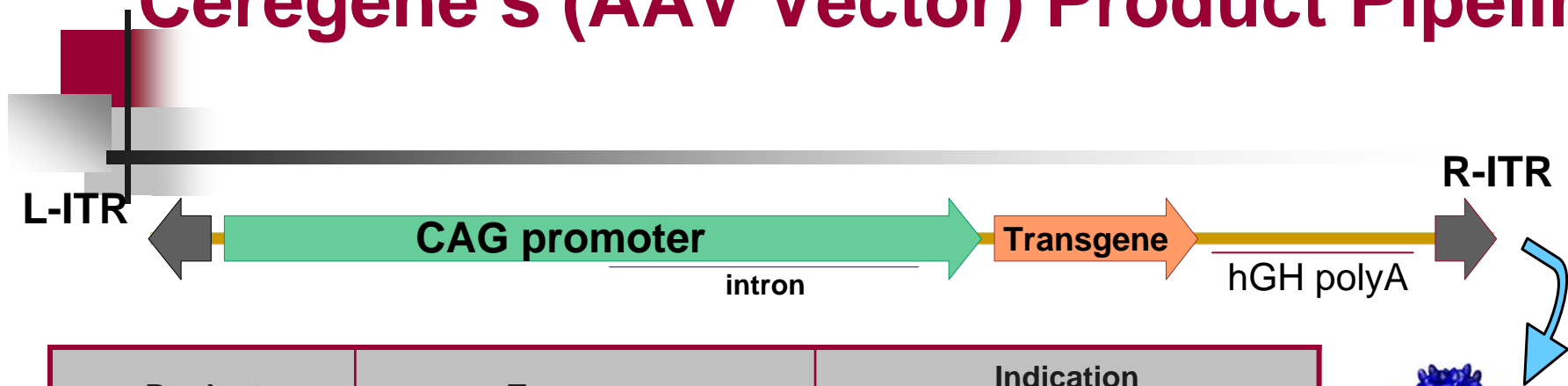
- Enrollment initiated: Dec 2006
- Enrollment completed: Oct 2007 (n=58)
- Top line data expected: near end of Dec 2008
 - Comparing CERE-120 treated versus sham surgery control subjects



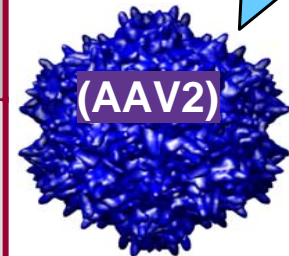
CERE-120 Summary

- Proof of principle for achieving persistent neurotrophic response achieved in multiple animal models
- Wide safety margin also established
- Preliminary Phase 1 data in PD patients supports possible efficacy and safety
- Properly controlled study enrolled; top line data available near end of year

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Major Colleagues/Collaborators for CERE-120 preclinical and/or clinical programs

C. Herzog, J. Ostrove, K. Bishop , M. Gasmi, ***Ceregene, Inc.***

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M. Tuszynski, ***University California at San Diego***

W. Olanow, ***Mt. Sinai School of Medicine*** (NYC)

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