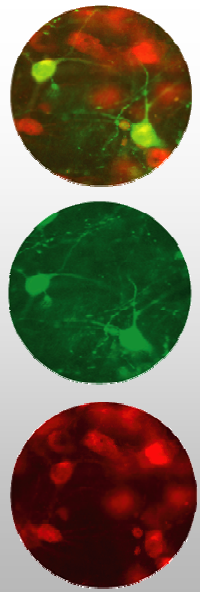
CERE-120 (AAV-Neurturin) for Parkinson's Disease



NIH OBA Protocol # 0501-689

A Phase I, Open-Label Study of CERE-120 (Adeno-Associated Virus Serotype 2 [AAV2]-Neurturin [NTN] to Assess the Safety and Tolerability of Intrastriatal Delivery to Subjects with Idiopathic Parkinson's Disease

CERE-120 Program Overview

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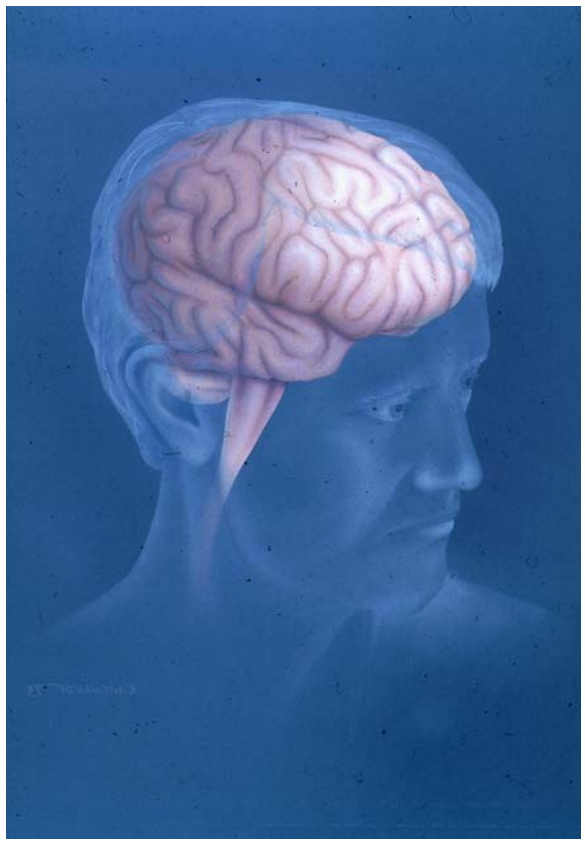
AAV-NTN: opportunity for innovative therapy for Parkinson's disease

- **Target dopamine nigrostriatal neurons:** degeneration implicated as key pathogenic event in disease
- Provide **constant supply of neurotrophic factor**
  - enhancing condition and function of neurons
  - strengthening their ability to withstand degeneration

Targeted neurotrophic factors should offer two benefits to Parkinson's patients

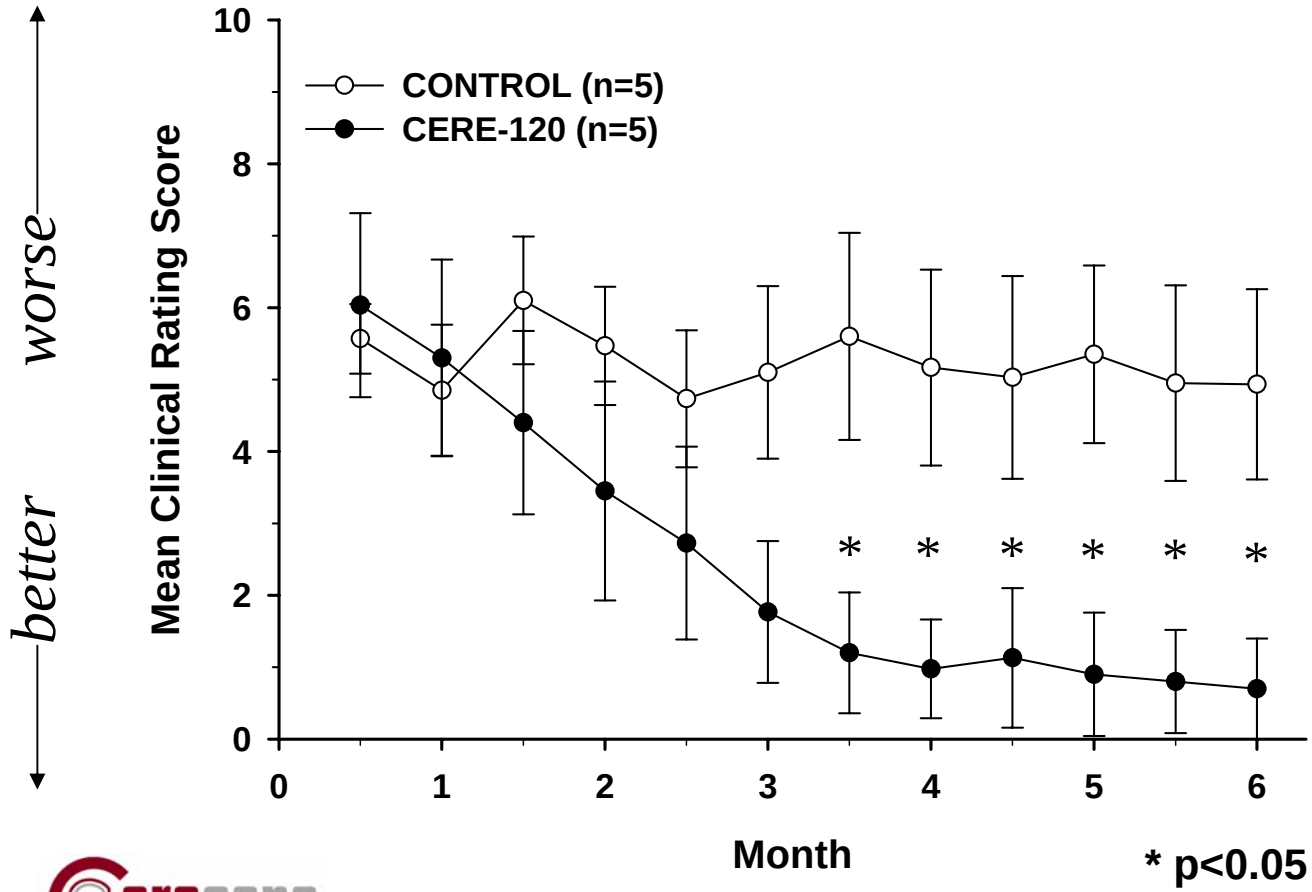


1) **Improve disease symptoms**
2) **Retard disease progression**

Most experts acknowledge that if these goals could be achieved…

…it would revolutionize the treatment of PD

AAV-NTN (CERE-120) produces functional improvement in MPTP lesioned monkeys over time



Potential advantages of AAV- NTN gene transfer for PD

- Employ **same AAV vector currently used in other CNS gene transfer trials**, including AAV-NGF (CERE-110) for AD
- Administer relatively **small quantities** of vector and transgene **directly** to **target**
- **Avoid significant systemic exposure** of vector and transgene

Controlling potential risks with innovative gene transfer for PD

- **Leverage** much of prior **experience** with delivering **neurotrophic factors** to the brains of animals and **humans**

- Deliver **NTN** gene, which is structurally and functionally **similar to GDNF**, which in turn, has been well-characterized and administered into human brain for years

- Execute **comprehensive safety/toxicology** program with high dose multiples

Overview: CERE-120 Nonclinical program, part 1

19 total studies (7 monkey and 12 rat studies, examining 45 monkeys and 384 rats) involving three different types of studies:

- Pharmacology
- Efficacy
- Safety/toxicology

- **Pharmacology** (established expression **kinetics, volume** of distribution & **dosing** relationships of CERE-120)
  - 4 Rat studies (82 rats)
  - 1 monkey study (3 monkeys)

Overview: CERE-120 Nonclinical program, part 2

- **Efficacy** (established **bioactivity/efficacy and dose-response** of NTN)
  - 3 Rat studies (109 rats)
  - 2 monkey studies (13 monkeys, including 3 aged)

- **Safety/toxicology** (established **wide safety margin** of CERE-120)
  - 5 rat studies (193 rats, including 25 aged)
  - 4 monkey studies (29 monkeys)

CERE-120 Safety Profile, part 1

- **Large dose multiples** were tested:
  - **Efficacious in rats at 125 fold lower** than highest (safe) toxicology dose
  - **Safe in monkeys at >100 and 400 fold higher** than proposed human doses

- **No overt, adverse effects**: body weight, appearance, general health and general behavior (rats: 12mos; monkeys: ~8mos)

- **No adverse effects** on formal **neurological or behavioral** assessments

CERE-120 Safety Profile, part 2

- **No functional impairments** on the targeted nigrostriatal system
- No **histopathological** changes in targeted **nigrostriatal system** or **cerebrum, cerebellum, brain stem, spinal cord** or any **peripheral organ**
- **No** adverse **effect on blood** clinical chemistry or hematology

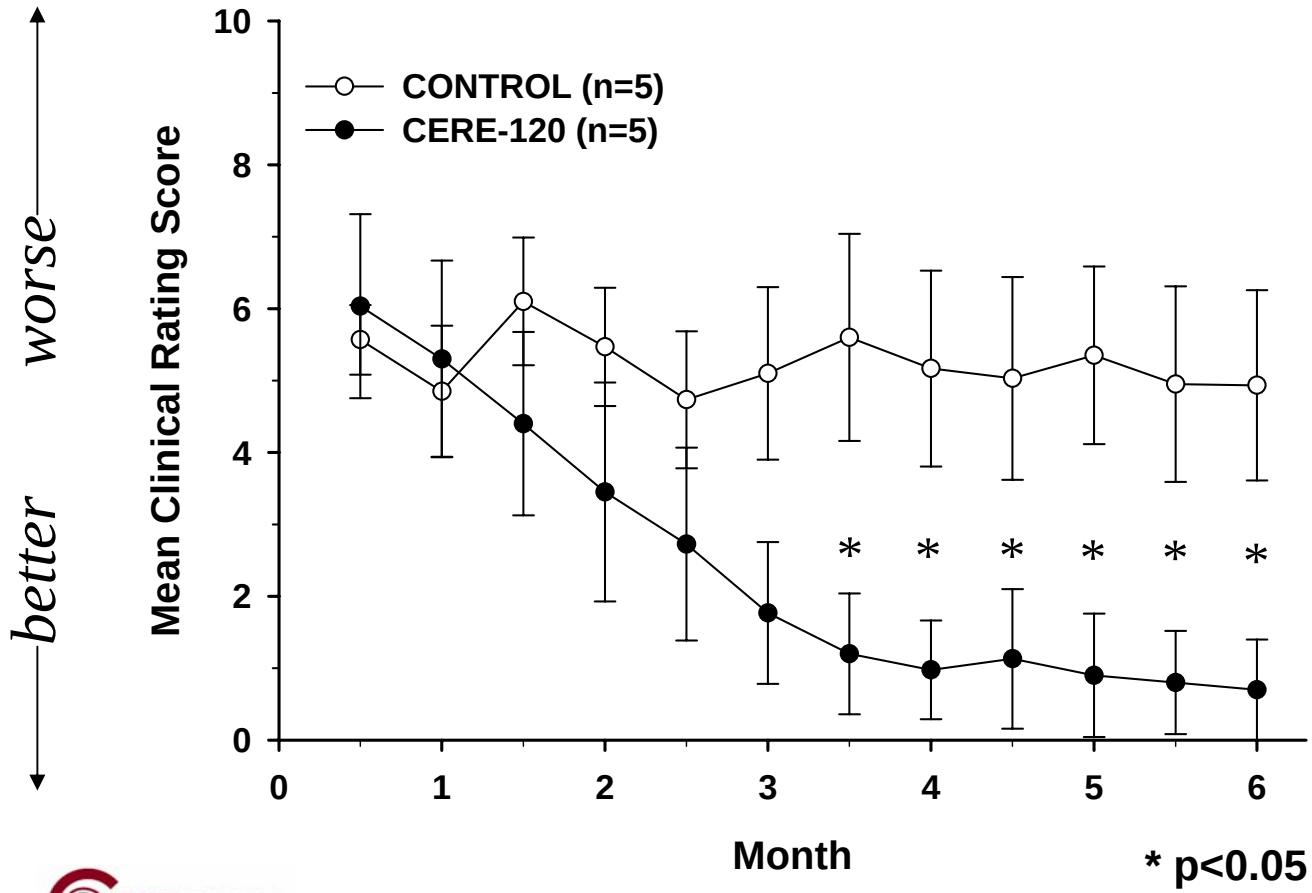
Bottom line: **No** sign of any **toxicity** of any kind, at very large dose multiples, over many months in **rats** and **monkeys**

Key RAC review points

1) Questions regarding efficacy of CERE-120
2) Kinetics and accumulation of NTN in brain
3) ‘Multiple brain regions’ targeted and spread of protein to non-targeted brain regions
4) The use of non-regulatable vector
5) Question of ‘rescue strategy’
6) Cerebellar toxicity reported in select, GDNF protein-treated monkeys
7) Rationale for dosing schedule in humans

Issue #1: Questions regarding efficacy of CERE-120

CERE-120 produces functional improvement in MPTP lesioned monkeys over time

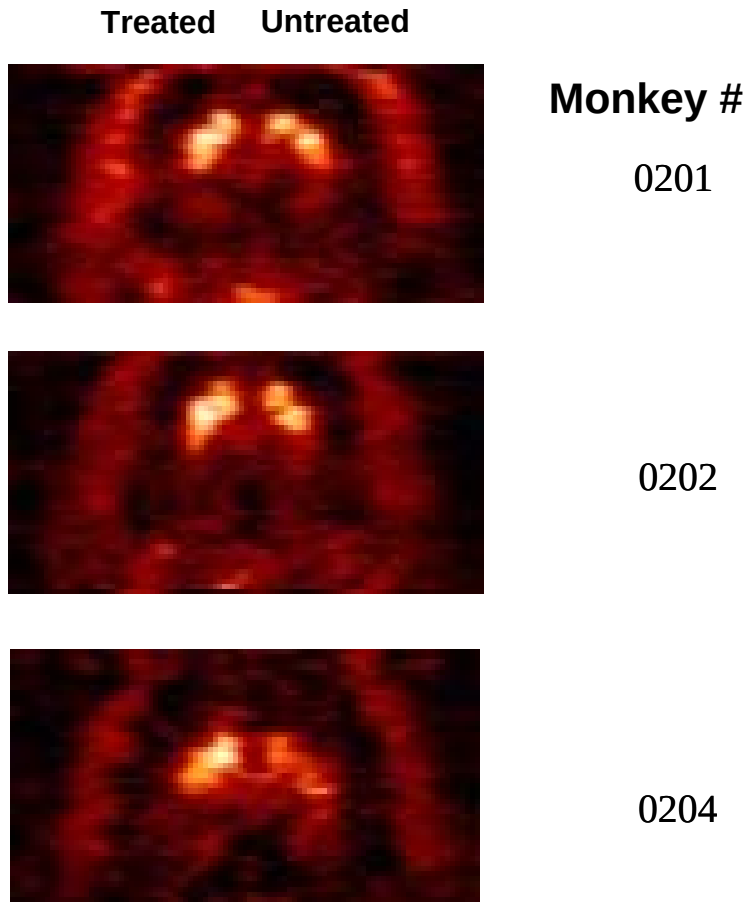


CERE-120 Enhances ^{18}F-Dopa in Striatum of Aged Monkey via PET

K_{OCC} values:

Monkey #	Treated hemisphere	Untreated hemisphere	% difference
0201	0.056	0.046	+19.6%
0202	0.065	0.055	+17.4%
0204	0.047	0.037	+26.6%
Mean	0.056±0.005	0.046±0.005	**+21.2%**

t(2)=39.74, p<0.001



CERE-120: multiple, mutually corroborating evidence of bioactivity/ efficacy

- Young, healthy monkeys
  - Enhanced **nigrostriatal TH** staining
  - enhanced **activation of pERK signaling**
- 6-OHDA rat model of PD
  - **Protection** of nigral cells at multiple time points (**up to 7 mos**)
  - **Protection** of nigral cells over **range of doses,** including **fraction of dose** shown to be **safe (**i.e. 1/125)
  - **Functional (behavioral) benefit**
- MPTP monkey model of PD
  - long-lasting **improvement in motor performance**
- Aged monkeys
  - **Enhanced ^{18}F-Dopa PET** update in striatum
- Aged rats *(New since filing App. M)*
  - 'Classic' **neurotrophic-induced hypertrophy**: dopamine nigra neurons

Issue #1: Questions regarding efficacy of CERE-120

Synopsis:

CERE-120 provides clear and consistent neurotrophic support for nigrostriatal neurons in multiple rat and monkey studies, including 'best models of PD'

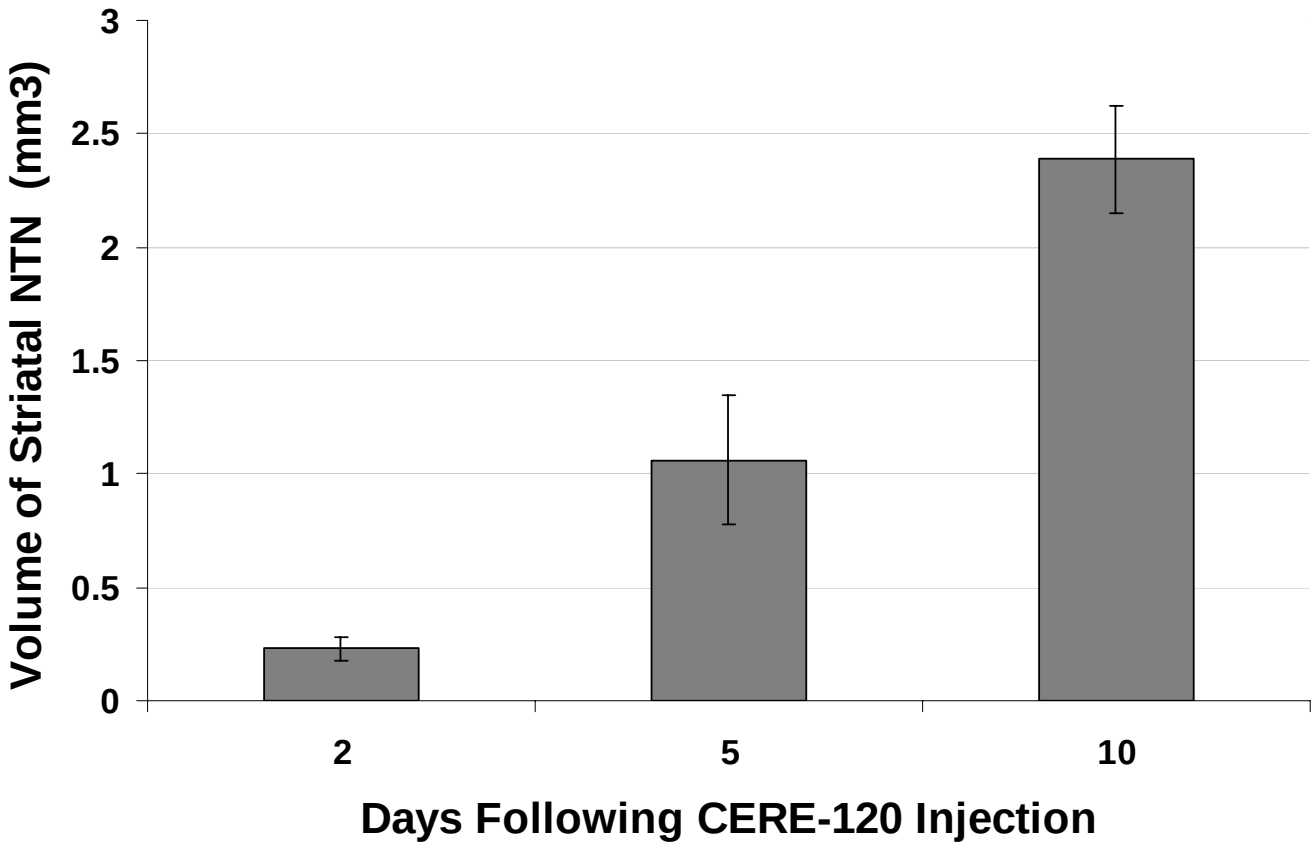
Issue #2: Kinetics and Accumulation of NTN in Brain

Summary: CERE-120 Pharmacology

- **NTN** is **expressed** in the rat striatum
  - as **early as 2 days**
  - approaches **asymptote** at approximately **4 weeks**
  - shows **no** significant **increases thereafter** (up to seven months)

- **NTN** volume of **distribution**
  - **controlled via dose** of CERE-120
  - shows **no** further **accumulation** over range of doses

NTN expression seen soon after CERE-120 administration



NTN volume of distribution is stable over time following AAV-NTN treatment in rats

Months: post CERE-120 injection	Volume of NTN distribution (mm^3)	
	Striatum	Total
1	14.84 ± 1.16	19.13 ±1.79
3	12.79 ± 1.12	16.85 ±1.86
6	11.08 ± 1.15	14.96 ±1.46
7	14.43 ± 1.47	ND

NOTE:

- **Total reflects sum of all NTN staining, including striatum and all surrounding areas, particularly the globus pallidus and cortex around needle track (only).**
- **ND: The total volume of NTN spread at 7 mo. was not determined.**
- **Data are derived from several separate experiments.**

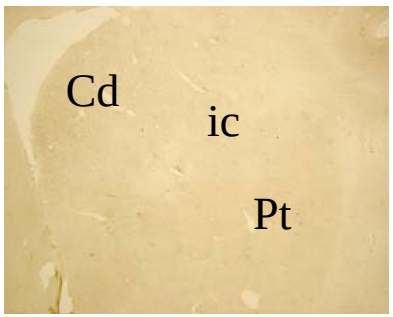
Issue #2: Kinetics and Accumulation of NTN in Brain

Synopsis:

- **Onset of NTN expression: rapid**
- **Volume of expression: reaches steady state levels at about 4 weeks and then shows no significant, further increase**
- **No accumulation during many months, over range of doses**

Issue #3: ‘Multiple Brain Regions’ Targeted and Spread of Protein to Non-targeted Brain Regions

Dose-related NTN distribution in monkey striatum



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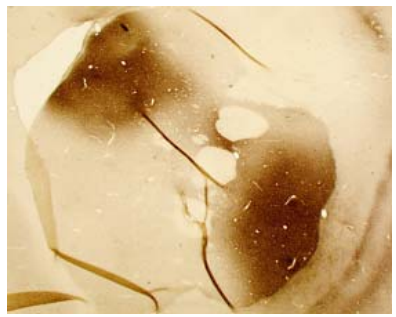
CERE-120
Low Dose
($3x10^{10}$ vg)

CERE-120
Mid Dose
($1x10^{11}$ vg)

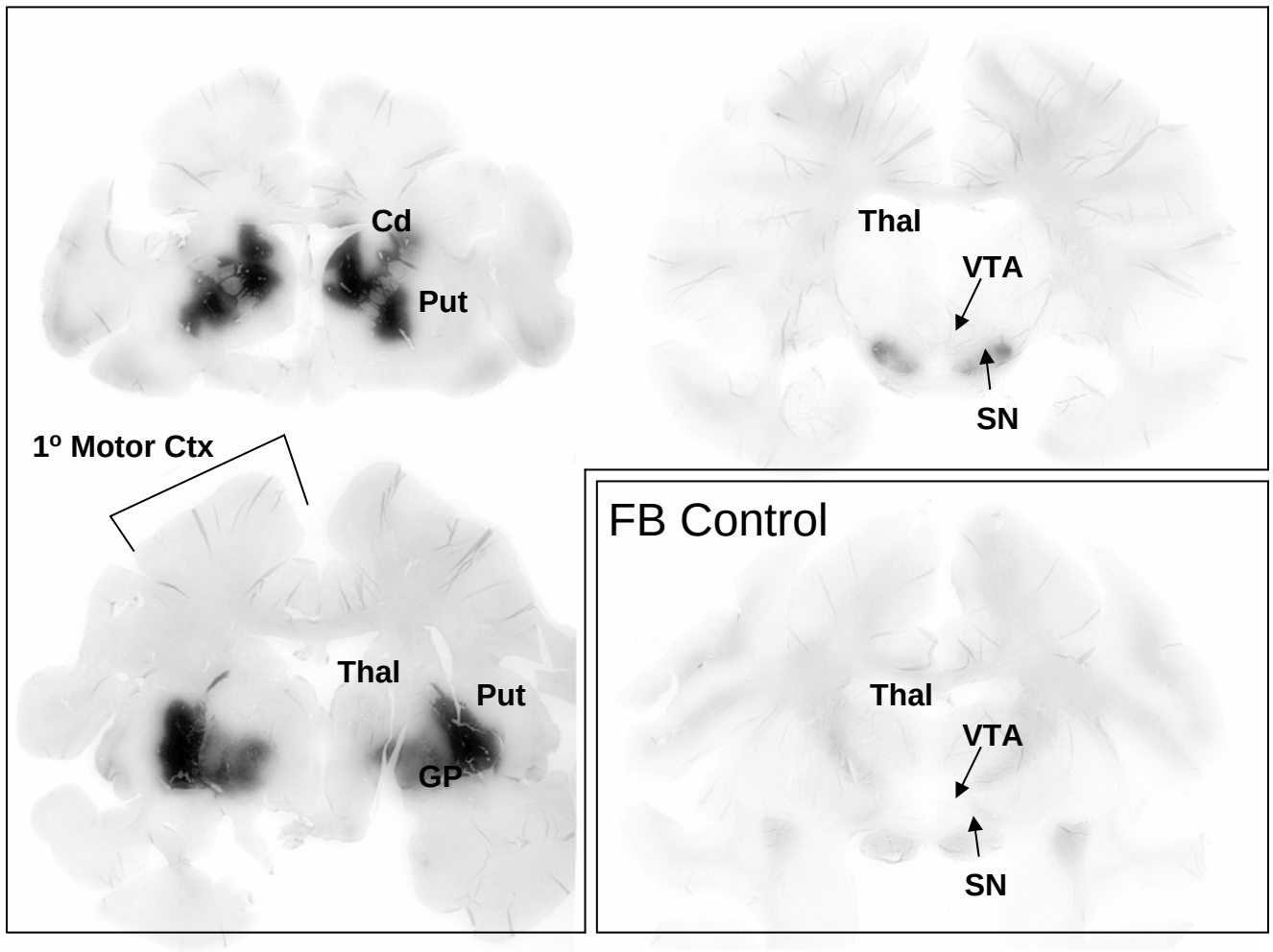


CERE-120
High Dose
($3x10^{11}$ vg)

Cd = caudate
ic = internal capsule
Pt = putamen

Doses: vg/hemisphere

Distribution of NTN in monkey following highest possible CERE-120 dose (1.75 x 10^{12} vg/hemi.)



Primate brain regions expressing NTN protein following CERE-120

Brain Region	*Dose*			
	6E10	2E11	6E11	1.75E12
Striatum	yes	yes	yes	yes
Substantia Nigra	yes	yes	yes	yes
Globus pallidus (neuropil/fibers only)	(yes)	(yes)	(yes)	(yes)
VTA	**NO**	**NO**	**NO**	**NO**
Thalamus	**NO**	**NO**	**NO**	**NO**
Cortex (excluding track)	**NO**	**NO**	**NO**	**NO**
Remainder of brain	**NO**	**NO**	**NO**	**NO**

Issue #3: 'Multiple Brain Regions' Targeted and Spread of Protein to Non-targeted Brain Regions

Synopsis:

Targeting of CERE-120 is limited to nigrostriatal system and NTN expression is mostly limited to this system, as well

Issue #4: The Use of Non-regulatable Vector

Perspectives on the general use of non-regulatable vectors for neurotrophic factors

- Several **human trials** already **delivered neurotrophic factors into CNS** (up to several years); risks appear well characterized and likely related to non-targeted delivery
- Several **gene therapy trials** previously approved by RAC for **heart and CNS** indications, delivered growth factors via non **regulatable vectors**
- **Regulatable vectors** have their own **potential risks** (e.g., **unnatural**, transcriptional **proteins** are persistently expressed **without regulation** and can generate **immune reaction**; i.e., the **regulator is unregulated**
- Unknown **risks** associated with small molecule regulator (i.e., systems inherently require additional '**regulator drug**')
- **No regulatable vector** has **yet** been tested **in humans** and a full assessment of efficacy & risks is still several years away

Justification for using a non- regulatable vector specifically to deliver NTN for PD

- **CERE-120** produces **no** apparent **toxicity**, including none of the empirically-defined effects of poorly targeted growth factors
- **Doses hundreds of times higher** than those proposed for this human trial were tested in animals, demonstrating that:
  - Expression of **protein** is mostly **restricted** to nigrostriatal system
  - **No** significant **increase in volume** of expression occurs after 4 weeks
  - **No adverse effects** are observed anywhere in the **CNS**
  - **No adverse effects** are seen anywhere **systemically**

CERE-120 dose multiples

- Rat dose multiple
  - Rat efficacious dose versus dose shown to be safe: **250 times**
- Rat to human dose multiple (via brain weight)
  - Dose shown to be safe versus proposed human doses: **50 and 200 times**
- Monkey to human dose multiple (brain weight)
  - Dose shown to be safe versus proposed human doses: **100 and 400 times**

Conclusion: Data support CERE-120 as a non-regulatable vector to deliver NTN for PD

- **Wide safety margin** of CERE-120 established, **without regulation**:
  - expression of protein is controlled
  - is stable from 1 month to > 7 months
  - is safe at large dose multiples
- Arguments against a regulatable vector:
  - an **appropriate risk: benefit** ratio established
  - regulatable vector **could** conceivably **increase risk** due to unknown aspects of more complicated, 'first in human' construct
  - **No prior studies required** a regulatable vector and the data with CERE-120 reveal no reason for greater concern

Issue #4: The Use of Non-regulatable Vector

Synopsis:

While concerns about unregulated expression of NTN may seem understandable, they are not supported by CERE-120 safety/distribution data and nature of proposed protocol

Issue #5: ‘Rescue Strategy’ Employed

Addressing Possible Adverse Events (AEs) to CERE-120

1) We carefully **considered possible** and hypothetical **AEs**, based on collective past experience with growth factors, nuances of Parkinson's disease & comprehensive review of literature
2) Are providing **clear information** regarding all potential & hypothetical risks to **each subject** via "informed consent"
3) Will continuously and **carefully monitor subjects** for AEs and manage with available therapy

Hypothetical AE's and Treatment Strategies

Symptoms	Setting / Liability	Treatment Options
Nausea & vomiting	**Only seen with ICV GDNF; delivery problem**	**Antiemetics (e.g., ondansetron; trimethobenzamide; domperidone)**
Anorexia & weight loss	**Only seen with ICV GDNF; delivery problem**	**•Clinical monitoring & diet change •Appetite enhancers**
Parethesias / Pain	**More severe with ICV GDNF; less with intraputaminal infusion; delivery problem**	**•NSAIDS & acetaminophen •Tricyclic antidepressants •Gabapentin &/or tizanidine**
Lhermitte's sign	**More severe with ICV GDNF; less with intraputaminal infusion**	**Pharmacological Rx (mexiletine; gabapentin; tizanidine; tricyclics)**
Hyponatremia	**Only seen with ICV GDNF; delivery problem**	**•Limit free water intake •Demeclocycline & lithium carbonate**
GI Disturbances	**Only seen with ICV GDNF; delivery problem**	**•Adjust diet; add bulking agents •RX: laxatives/soften stool; diarrhea**
Dsykinesias	***Hypothetical AE:* GDNF actually appears to *reduce* dyskinesias**	**•Adjust antidopaminergic therapy •Add amantadine •Deep brain stimulation**
Psychotic symptoms	***Hypothetical AE*: No empirical data**	**•Adjust dopaminergic therapy •Add atypical anti-psychotics**

Issue #5: ‘Rescue Strategy’ Employed

Synopsis:

Rescue strategies do exist to deal with hypothetical risks of CERE-120

Issue #6: Cerebellar Toxicity Reported in Select, GDNF-treated Monkeys

Synopsis of GDNF-induced ‘Cerebellar Toxicity’

- Toxicity reported: **focal cell loss in cerebellum** of some of ‘ 6mo highest dose- 3 mo recovery’ monkeys (only)
- If link between GDNF and cytotoxicity is proven, data suggests it was **likely caused** by deficiencies in delivery system (i.e., **leakage of protein from indwelling cannula**); supported by:
  - Clear evidence of ‘classic’ changes near meninges (e.g, pia thickening, Schwann cell hyperplasia and sympathetic in growth; Boyd & Hovland, 2004) in mid and high dose monkeys
  - Confirmation of I^{125}-GDNF in occipital cortex and cerebellum in monkeys infused using similar pump/cannula system (Gash et al, 2005)

Synopsis of GDNF-induced 'Cerebellar Toxicity': part 2

- Evidence of leakage (and possible toxicity) **reinforces need** for **improved delivery** method
  - Gill, et al (Nat Med, 2003) suggested **gene therapy** as example of improved delivery method
  - No **evidence for protein leakage or cerebellar cytotoxicity** following very high doses of **CERE-120** in rats or monkeys
- **Subjects** in GDNF studies: **no** apparent **cerebellar AEs**
  - Initial autopsy subject from Gill et al study revealed no cerebellar toxicity

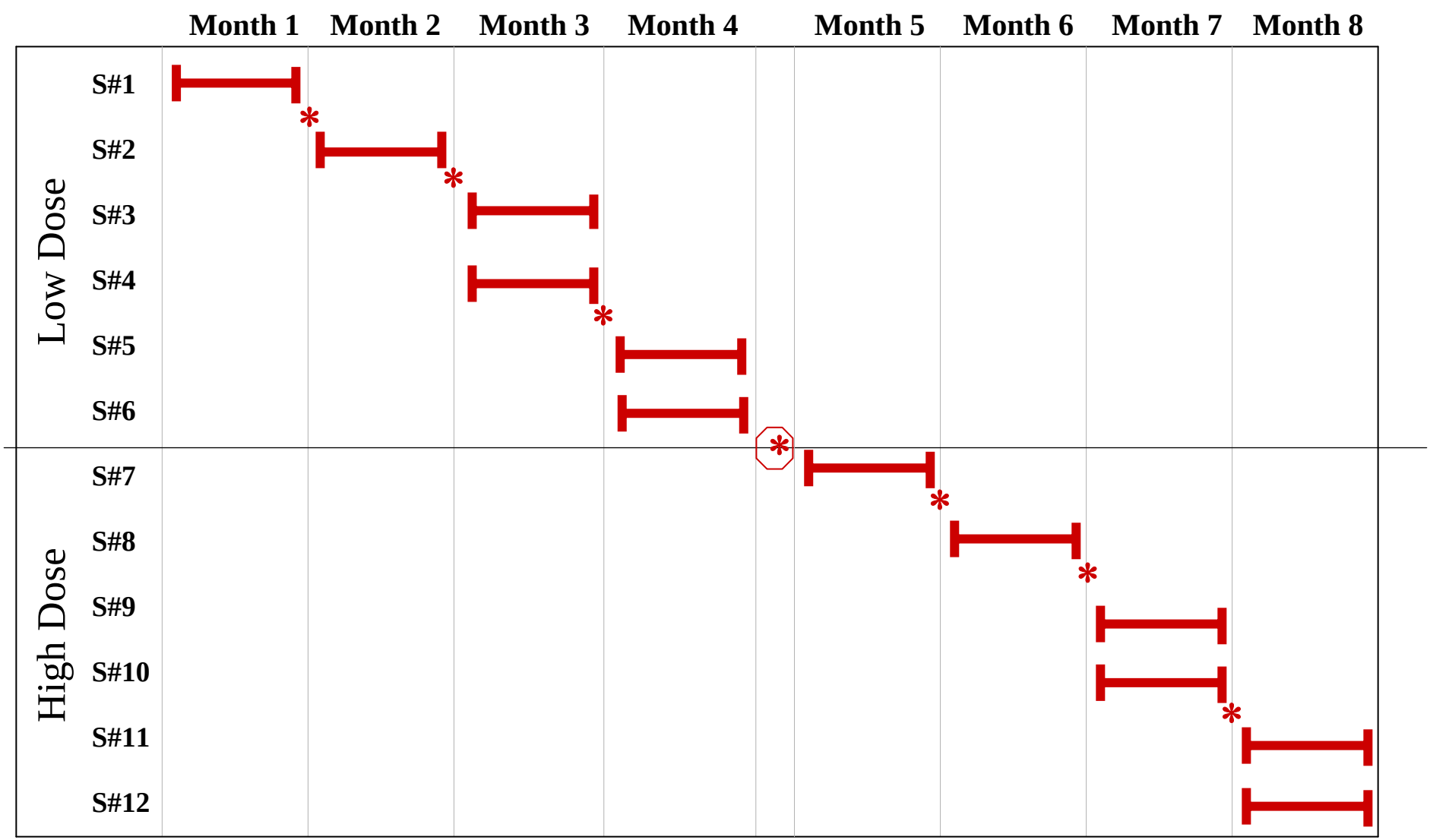
Issue #6: Cerebellar Toxicity Reported in Select, GDNF-treated Monkeys

Synopsis:

Putative GDNF toxicity most likely reflects untargeted delivery in monkeys and not inherent limitation of protein- this argues FOR, NOT AGAINST use of gene transfer for this application

Issue #7: Rationale for Dosing Schedule in Humans

Schematic of Proposed Dosing Schedule for CERE-120



*** DSMB Cumulative Data Review**

Rationale for CERE-120 Dosing Schedule in Advanced PD subjects

- Purpose of this study is to evaluate safety of CERE-120
- **Volume of expression** of NTN occurs early and has reached **steady** state by **four weeks**
- The **nonclinical package** reveals an ‘uneventful’ **safety**/tox profile, at very **high dose multiples**, following **many months** of treatment in both rats and monkeys
  - No evidence of toxicity observed and no evidence of greater risk over time

Rationale for CERE-120 Dosing Schedule in Advanced PD subjects (cont.)

- Protocol ‘leverages’ decades of **experience** gained with **growth factors** in animals and **humans** (scores of patients dosed up to several years each)
- Those studies suggest **greatest risk** for toxic effects (humans and animals) is **untargeted delivery** and these effects typically appear within days to < four weeks
- **Hypothetical risk** with gene transfer: **uncontrolled spread** of protein to ventricles. **Data** for CERE-120 (volume of distribution with large dose multiples over many months) convincingly argue that this is extremely unlikely with proposed human doses

Issue #7: Rationale for Dosing Schedule in Humans

Synopsis:

- Proposed dosing schedule supported by:
  - Data generated for CERE-120, as well as, that for neurotrophic factors, generally
  - Need to find more effective treatments for advanced PD patients
  - Careful safety monitoring proposed

Specific issues raised in RAC review deserving special comment

1) Evidence of efficacy of CERE-120
2) Kinetics and accumulation of NTN in brain
3) ‘Multiple brain regions’ targeted and spread of protein to non-targeted brain regions
4) The use of non-regulatable vector
5) Question of ‘rescue strategy’
6) Cerebellar toxicity reported in select, GDNF-treated monkeys
7) Rationale for dosing schedule in humans