



# Corporate Presentation

July 2019



# Forward-Looking Statements

This presentation contains forward-looking statements for the purposes of the safe harbor provisions under The Private Securities Litigation Reform Act of 1995 and other federal securities laws. The use of words such as “may,” “might,” “will,” “should,” “expect,” “plan,” “anticipate,” “believe,” “estimate,” “undoubtedly,” “project,” “intend,” “future,” “potential,” or “continue,” and other similar expressions are intended to identify forward-looking statements. For example, all statements Voyager makes regarding the initiation, timing, progress and reporting of results of its preclinical programs and clinical trials and its research and development programs, its ability to advance its AAV-based gene therapies into, and successfully initiate, enroll and complete, clinical trials, the potential clinical utility of its product candidates, its ability to continue to develop its product engine, its ability to enter into new partnerships or collaborations, its anticipation for the timing or likelihood of its regulatory filings and approvals, are forward looking. All forward-looking statements are based on estimates and assumptions by Voyager’s management that, although Voyager believes to be reasonable, are inherently uncertain. All forward-looking statements are subject to risks and uncertainties that may cause actual results to differ materially from those that Voyager expected. Such risks and uncertainties include, among others, those related to the initiation and conduct of preclinical studies and clinical trials, the availability of data from clinical trials and the expectations for regulatory submissions and approvals; the continued development of the product engine; Voyager’s scientific approach and general development progress; the availability or commercial potential of Voyager’s product candidates; the sufficiency of cash resources; and need for additional financing. These statements are also subject to a number of material risks and uncertainties that are described in Voyager’s most recent Annual Report on Form 10-K filed with the Securities and Exchange Commission, as updated by its subsequent filings with the Securities and Exchange Commission. Any forward-looking statement speaks only as of the date on which it was made. Voyager undertakes no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events or otherwise, except as required by law.

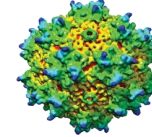
This presentation also contains estimates and other statistical data made by independent parties and by the Company relating to market size and growth and other data about the Company's industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions and estimates of the Company's future performance and the future performance of the markets in which the Company operates are necessarily subject to a high degree of uncertainty and risk.

# Convergence of Neuroscience and Gene Therapy



## Severe Neurological Diseases

- **Genetically-validated targets** with significant unmet medical need
- **Targeted delivery** to regions of the brain and spinal cord
- **Durable transgene** expression as CNS neurons are terminally differentiated
- **Immune-privileged** site reduces risk of immune response



## AAV Gene Therapy

- **Tissue and cell-specific targeting** within the CNS
- **No AAV-related SAEs** to date in >200 patients treated in CNS <sup>1</sup>
- **Does not readily integrate** into the target cell genome, reducing potential for oncogenesis
- **Ability to manufacture** at commercial quality and scale

Voyager

(1) Includes patients treated in Voyager's and other companies' clinical trials

# Strategic Collaborations Overview



NBIX holds development and commercialization rights to VY-AADC, VY-FXN01 and two additional programs to be determined

## **VYGR receives:**

- \$165 million upfront and up to \$1.7 billion in potential development, regulatory and commercial milestone payments, as well as tiered royalties on net sales
- Funding for all ongoing development costs for each program up until opt-in decisions
- Ability to opt-in for U.S. co-commercialization rights to VY-AADC and VY-FXN01 under a cost- and profit-sharing arrangement



Development of vectorized antibodies targeting Tau for Alzheimer's disease and other tauopathies and targeting Alpha-Synuclein for Parkinson's disease and other synucleinopathies

## **VYGR receives:**

- \$134 million combined upfront and up to \$460 million in preclinical and Phase 1 option payments
- For the vectorized tau antibody collaboration, \$895 million in potential development and commercial milestones and tiered royalties on the global net sales
- For the vectorized alpha-synuclein antibody collaboration, \$728 million in potential development milestones, \$500 million in potential commercial milestones and tiered royalties on the global net sales






# Restructuring of Sanofi Genzyme Relationship



## Key terms:

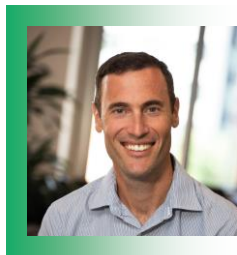
- Voyager gains worldwide rights to the VY-HTT01 Huntington's disease program
- Voyager gains ex-U.S. rights to the VY-FXN01 Friedreich's ataxia program, which are assigned to Neurocrine Biosciences
- Sanofi Genzyme's option to acquire development and commercialization rights to a future Voyager CNS orphan program is terminated
- Sanofi Genzyme receives options to Voyager owned or controlled capsids for exclusive use in up to two non-CNS indications
- Voyager to receive \$5 million from Neurocrine Biosciences for the transfer of the ex-U.S. rights to the VY-FXN01 program
- Voyager pays \$10 million to Sanofi Genzyme up front and an additional \$10 million upon the potential filing of an IND for the VY-HTT01 program
- Voyager is entitled to receive option exercise fees, milestone payments, and royalties on worldwide net sales by Sanofi Genzyme of products containing licensed capsids

# AAV Pipeline Focused on Severe Neurological Diseases

Program	Preclinical/Lead Candidate Selection	Phase 1	Phase 2-3
VY-AADC <sup>(1)</sup>	Parkinson's Disease		 Co-develop, co-commercialize
VY-HTT01	Huntington's Disease		
VY-SOD102 <sup>(2)</sup>	Monogenic form of ALS		
VY-FXN01 <sup>(1)</sup>	Friedreich's Ataxia	 Co-develop, co-commercialize	
Tau and Alpha-synuclein programs	Alzheimer's disease, PSP, FTD, PD, synucleinopathies <sup>(3)</sup>		
Early Pipeline	Undisclosed		

(1) Voyager has option to co-commercialize U.S. or grant Neurocrine global commercial rights (2) Voyager intends to seek a partner to advance (3) PSP = Progressive Supranuclear Palsy, FTD = Frontotemporal Dementia, PD=Parkinson's disease

# Senior Executive Team With Deep Experience



**Andre Turenne**  
President & Chief Executive Officer



**Omar Khwaja, M.D., Ph.D.**  
Chief Medical Officer and Head of  
Research and Development



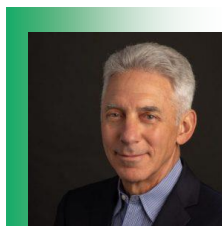
Boston  
Children's  
Hospital



HARVARD  
MEDICAL SCHOOL



**Matthew Ottmer**  
Chief Operating Officer



**Robert Hesslein**  
General Counsel



**Luis Maranga Ph.D.**  
Chief Technical Operations Officer



Bristol-Myers Squibb

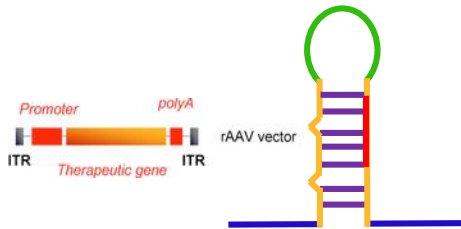


**Allison Dorval**  
Chief Financial Officer



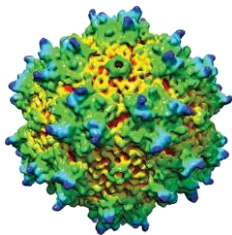
# Gene Therapy Development Requires Multiple Optimizations

*“Right Tissue, Right Cells, Right Amount, Right Time”*



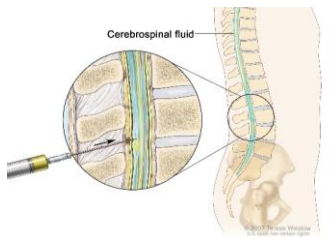
## Vector Genome Design

Transgene sequence & promoter selection for potent and selective pharmacology in target tissue



## AAV Capsid Selection

Tropism for relevant tissue and cell types



## Delivery Optimization

Translatable dosing paradigm that provides target distribution profile in relevant tissues





# VY-AADC for Parkinson's Disease



# Parkinson's Disease Overview

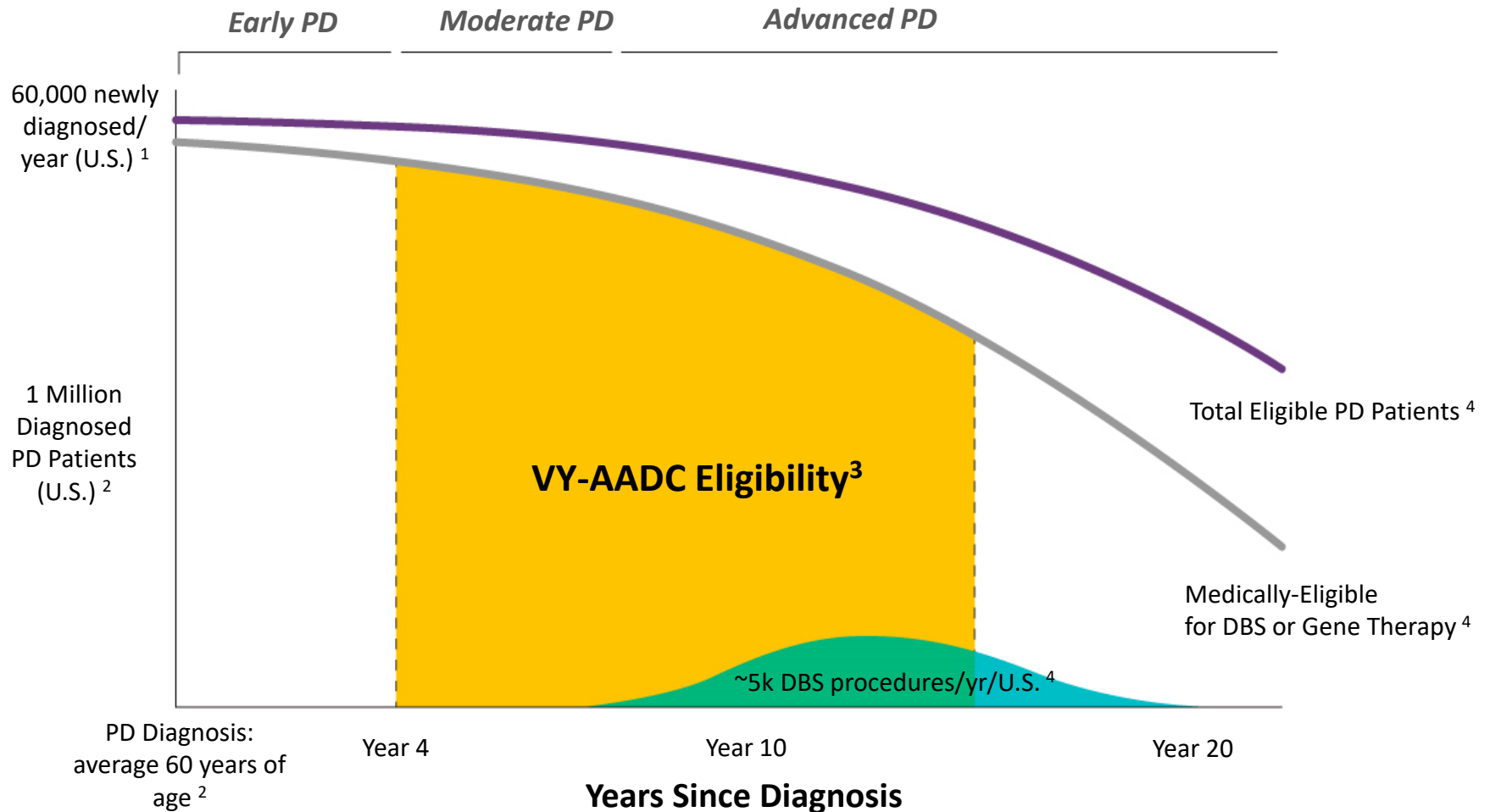
~1 Million/6 Million affected  
(U.S./WW)<sup>1</sup>

- Loss of neurons and critical AADC enzyme in the midbrain that produce dopamine leads to progressive loss of motor function and less responsiveness to levodopa
- Severe, debilitating loss of motor function including rigidity, postural instability, gait freezing, and difficulty with speech and swallowing
- One-time treatment with VY-AADC restores AADC enzyme activity and improves levodopa sensitivity with potential to improve clinical motor function



(1) Michael J. Fox Foundation

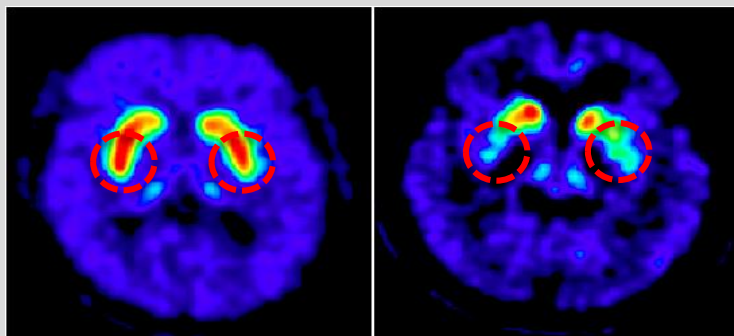
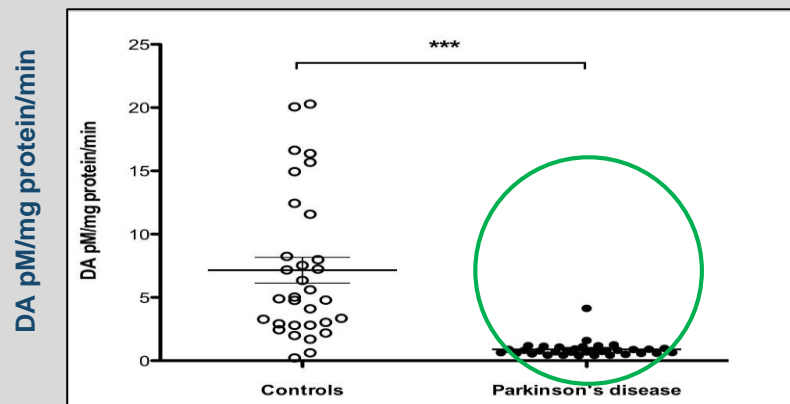
# Large Unmet Need in Moderate to Advanced PD



- (1) Parkinson.org
- (2) Michael J. Fox Foundation
- (3) VY-AADC Phase 2 eligibility > 4 years since diagnosis > 3 hours diary OFF time
- (4) Voyager estimates

# Declining AADC Activity Correlates with Declining Motor Function

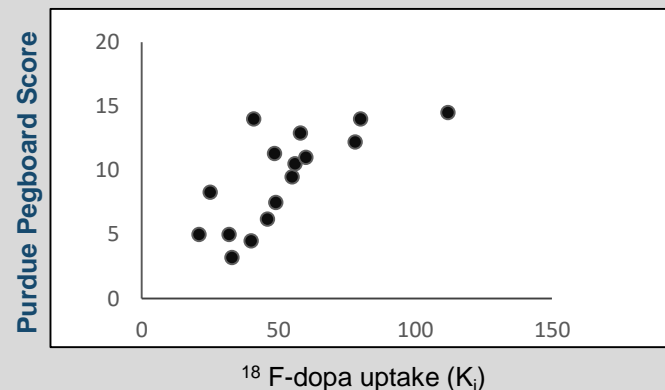
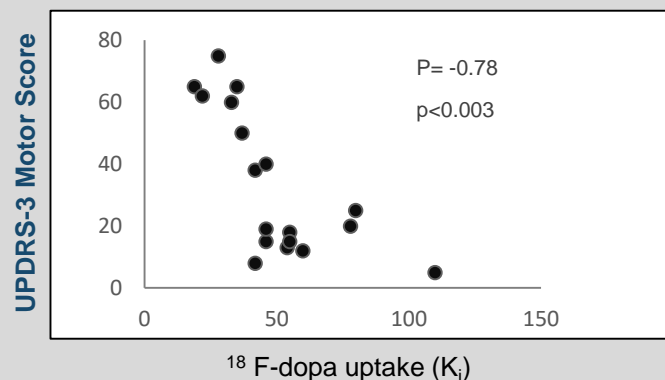
AADC activity in the Putamen<sup>(1)</sup>



Control<sup>(2)</sup>

PD patient<sup>(2)</sup>

AADC activity in the Putamen<sup>(1)</sup>



**Very little AADC activity** in the brains of patients with advanced PD compared to healthy people

**Lower AADC activity** correlates with worse **motor** symptoms and vice versa

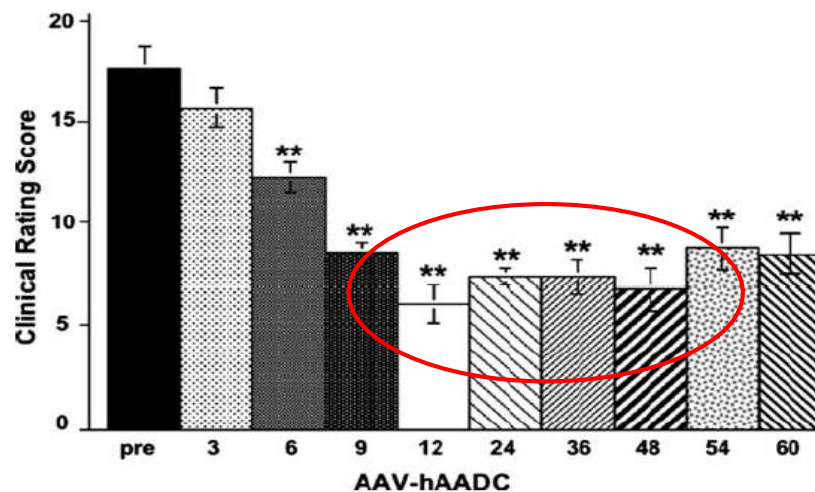
(1) K. Bankiewicz, Ribeiro (2002)

(2) Feinstein Institute for Biomedical Research

# AAV2-AADC: Dose and Temporal Response in NHPs

*Clinical rating scores improves over 12 months in response to AADC and is durable*

***Response to 3 mg/kg Levodopa Improves over 12 months and is Durable***



Bankiewicz, 2006



# Durable AADC Enzyme Expression/Motor Function Response

5 years

10 years

15 years

AADC  
Expression<sup>1</sup>

AADC  
Expression  
Motor Function  
Improvement<sup>2</sup>

AADC Expression  
Motor Function  
Improvement<sup>3</sup>

AADC  
Expression  
Motor Function  
Improvement<sup>4</sup>

**Persistent Expression of Dopamine-Synthesizing Enzymes 15 Years After Gene Transfer in a Primate Model of Parkinson's Disease**

Yoshihide Sehara,<sup>1</sup> Ken-ichi Fujimoto,<sup>2</sup> Kunihiro Ikeguchi,<sup>2</sup> Yuko Katakai,<sup>3</sup> Fumiko Ono,<sup>4</sup> Naomi Takino,<sup>5</sup> Mika Ito,<sup>5</sup> Keiya Ozawa,<sup>6</sup> and Shin-ichi

**Eight Years of Clinical Improvement in MPTP-Lesioned Primates After Gene Therapy With AAV2-hAADC**  
Piotr Hadaczek<sup>1</sup>, Jamie L. Eastling<sup>1</sup>, Philip Pivrotto<sup>1</sup>, John Bringas<sup>1</sup>, John Forsayeth<sup>1</sup> and Krystof S Bankiewicz<sup>1</sup>

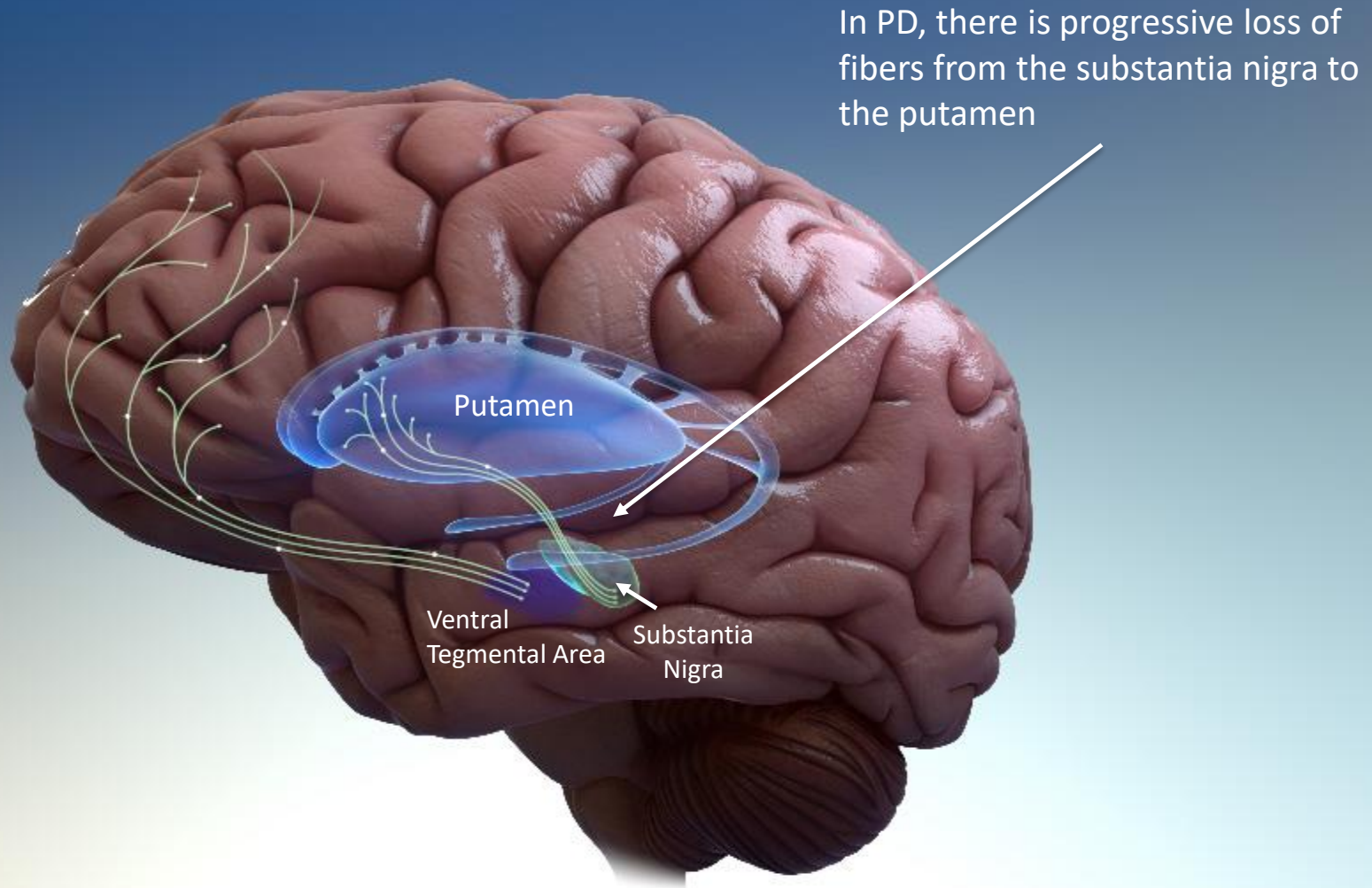
**Safety and tolerability of putaminal AADC gene therapy for Parkinson disease**  
C.W. Christine, MD, P.A. Starr, MD, P.S. Larson, MD, J.L. Eberling, PhD, W.J. Jagust, MD, R.A. Hawkins, PhD, H.F. VanBrocklin, PhD, J.F. Wright, PhD, K.S. Bankiewicz, PhD, M.J. Aminoff, MD



**Duration of measured expression/function response**

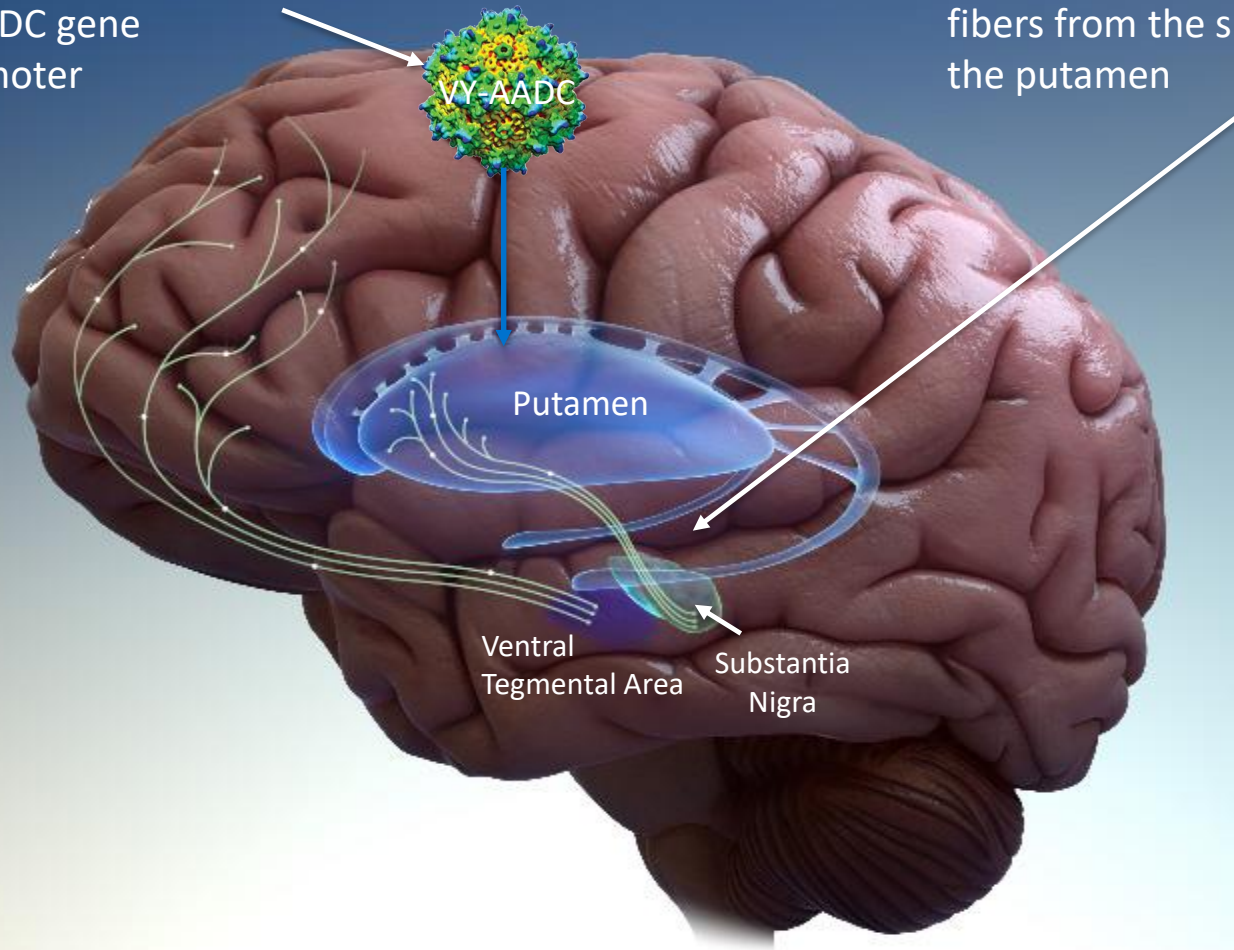
- (1) Sehara, Y, et al. (2017) *Human Gene Therapy Clinical Development*, Vol 28
- (2) Hadaczek, P, ASGCT, [www.moleculartherapy.org](http://www.moleculartherapy.org). 2010, Vol 18
- (3) Christine, CW, *Neurology*, 2009, Vol 73
- (4) Voyager ongoing Phase 1b trial

# The Ability to Make AADC is Lost as PD Advances

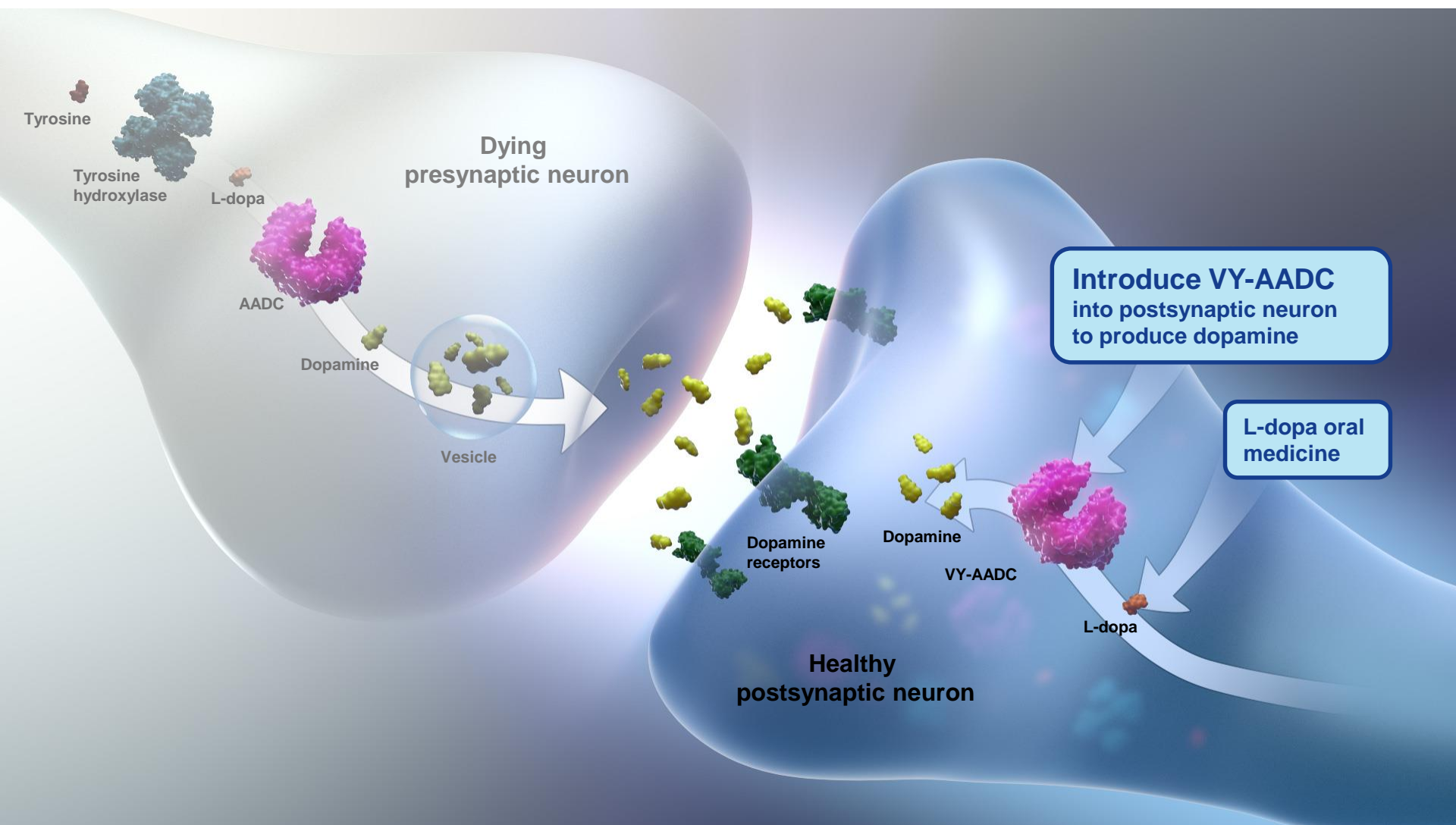


# Introduce AADC to Healthy Postsynaptic Neurons in the Putamen

- AAV-2 Capsid/Recombinant
- cDNA of the AADC gene
- CMV early promoter



# The Role of the AADC Enzyme



# Key Phase 1b (PD-1101) Objectives with VY-AADC

## 1. Exposure:

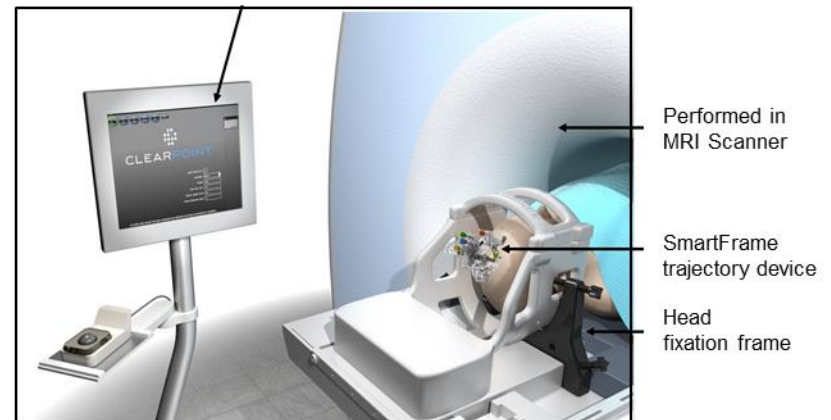
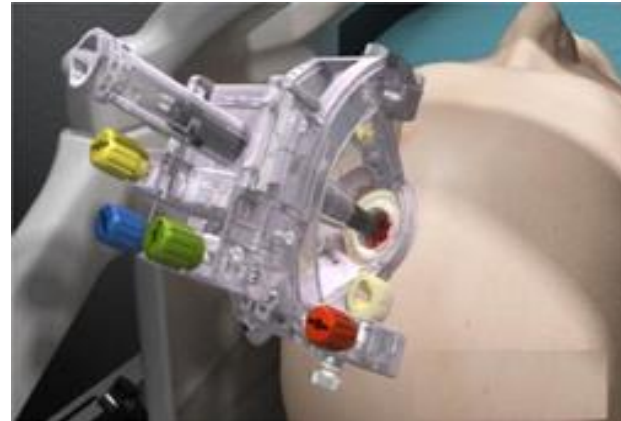
- Safely achieve  $\geq 30\%$  coverage of the putamen with MRI-guided infusions

## 2. Target engagement and pharmacology:

- Obtain increased enzyme activity with  $^{18}\text{F}$ dopa and PET
- Achieve enhanced response to levodopa through decreased dose requirements and response to IV levodopa

## 3. Clinical profile:

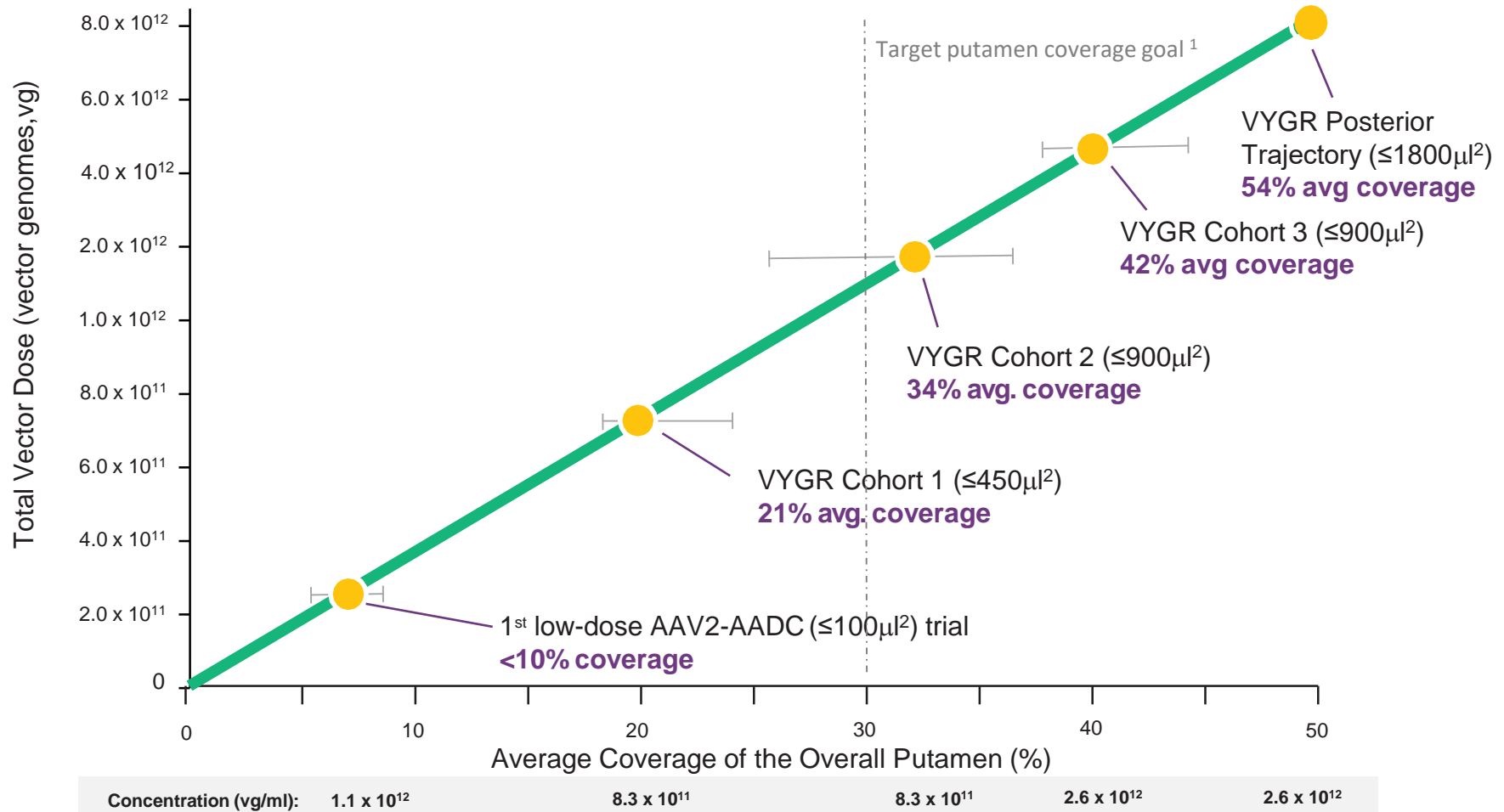
- Achieve dose and temporal responses across key clinical endpoints



Source: MRI Interventions



# Thorough Phase 1b Dose Escalation



Source: Christine, CW. Neurology 2009; 73:1662-1669, Voyager Therapeutics June 22, 2016 and January 20, 2017 press releases

(1) Target putamen coverage goal based on preclinical data from non-human primates

(2) Volume of infusion per putamen

# Phase 1b Trial Results Published in *Annals of Neurology*

Annals of  
NEUROLOGY

An Official Journal of  
the American Neurological  
Association and the  
Child Neurology Society



AMERICAN  
NEUROLOGICAL  
ASSOCIATION  
INNOVATORS IN DISCOVERY,  
EDUCATION, AND CARE



## **Magnetic Resonance Imaging–Guided Phase 1 Trial of Putaminal AADC Gene Therapy for Parkinson's Disease**

*MRI-guided administration of ascending VY-AADC01 doses resulted in putaminal coverage of 21% (cohort 1), 34% (cohort 2), and 42% (cohort 3). Cohorts 1, 2, and 3 showed corresponding increases in enzyme activity assessed by PET of 13%, 56%, and 79%, and reductions in antiparkinsonian medication of –15%, –33%, and –42%, respectively, at 6 months. At 12 months, there were dose-related improvements in clinical outcomes, including increases in patient-reported ON-time without troublesome dyskinesia (1.6, 3.3, and 1.5 hours, respectively) and quality of life.*

Christine, C. W., et al., (2019), Magnetic Resonance Imaging–Guided Phase 1 Trial of Putaminal AADC Gene Therapy for Parkinson's Disease. *Ann Neurol*. doi:10.1002/ana.25450

# VY-AADC Phase 1b Baseline Characteristics

*Patients representative of advanced stages of Parkinson's disease population*

	Cohort 1 (PD-1101)	Cohort 2 (PD-1101)	Cohort 3 (PD-1101)	Posterior Trajectory (PD- 1102)
Age	57.4 (7.2)	58.4 (8.6)	57.4 (4.5)	56.8 (3.9)
Sex	1 Female, 4 Male	5 Male	1 Female, 4 Male	1 Female, 7 Male
PD Duration (years)	9.9 (4.6)	10.1 (1.6)	8.5 (3.6)	9.2 (2.1)
UPDRS II off	13.6 (2.1)	16.0 (1.7)	19.8 (7.8)	15.3 (2.1)
UPDRS II on	3.0 (2.9)	3.6 (1.7)	5.0 (3.9)	3.5 (1.5)
UPDRS III off	37.2 (5.9)	35.8 (7.6)	38.2 (9.7)	34.9 (1.8)
UPDRS III on	7.6 (5.1)	17.0 (3.8)	16.0 (3.1)	11.4 (2.1)
Diary OFF time (hrs)	4.9 (1.7)	4.2 (1.4)	4.7 (1.2)	6.8 (0.6)
Diary good ON time (hrs)	10.5 (1.0)	10.6 (0.8)	10.3 (0.7)	9.1 (1.5)
Hoehn and Yahr Stage	3.0 (0.0)	3.0 (0.0)	3.4 (0.49)	2.8 (0.27)
UDysRS Total Score	19.2 (6.0)	17.4 (5.6)	30.2 (3.9)	22.8 (4.8)
LED <sup>(1)</sup> mg	1467.5 (615.0)	1635.5 (687.3)	1476.5 (429.1)	1500.9 (179.2)

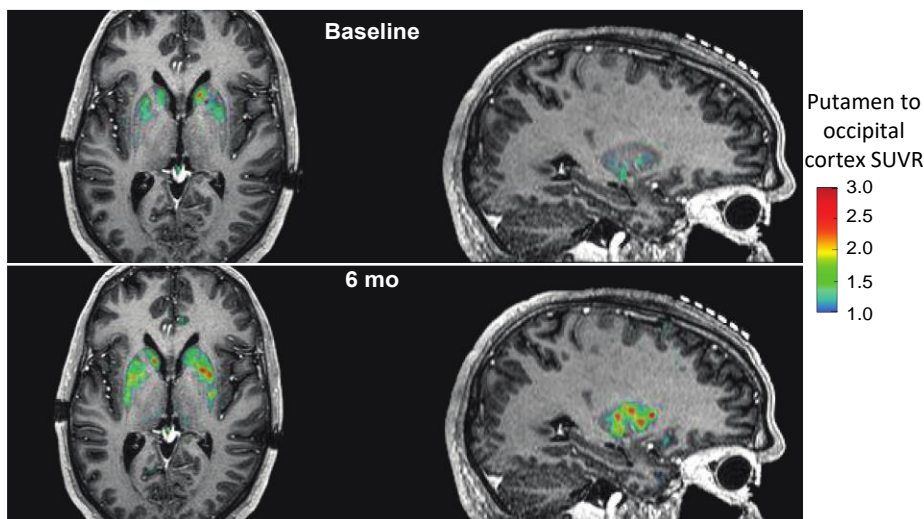
Source: Voyager Therapeutics and Christine, C. W., et al., (2019), Ann Neurol. doi:10.1002/ana.25450, and AAN 2019 Van Laar Poster

(1) Levodopa Equivalent Dose

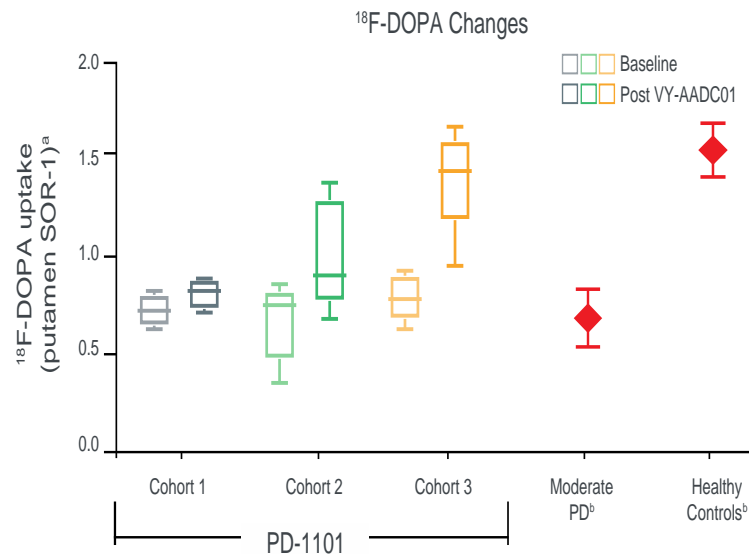
Mean (standard deviation)

# Change in AADC Activity in the Putamen

*Increased AADC Enzyme Activity Detected by PET Imaging and F-Dopa Uptake*



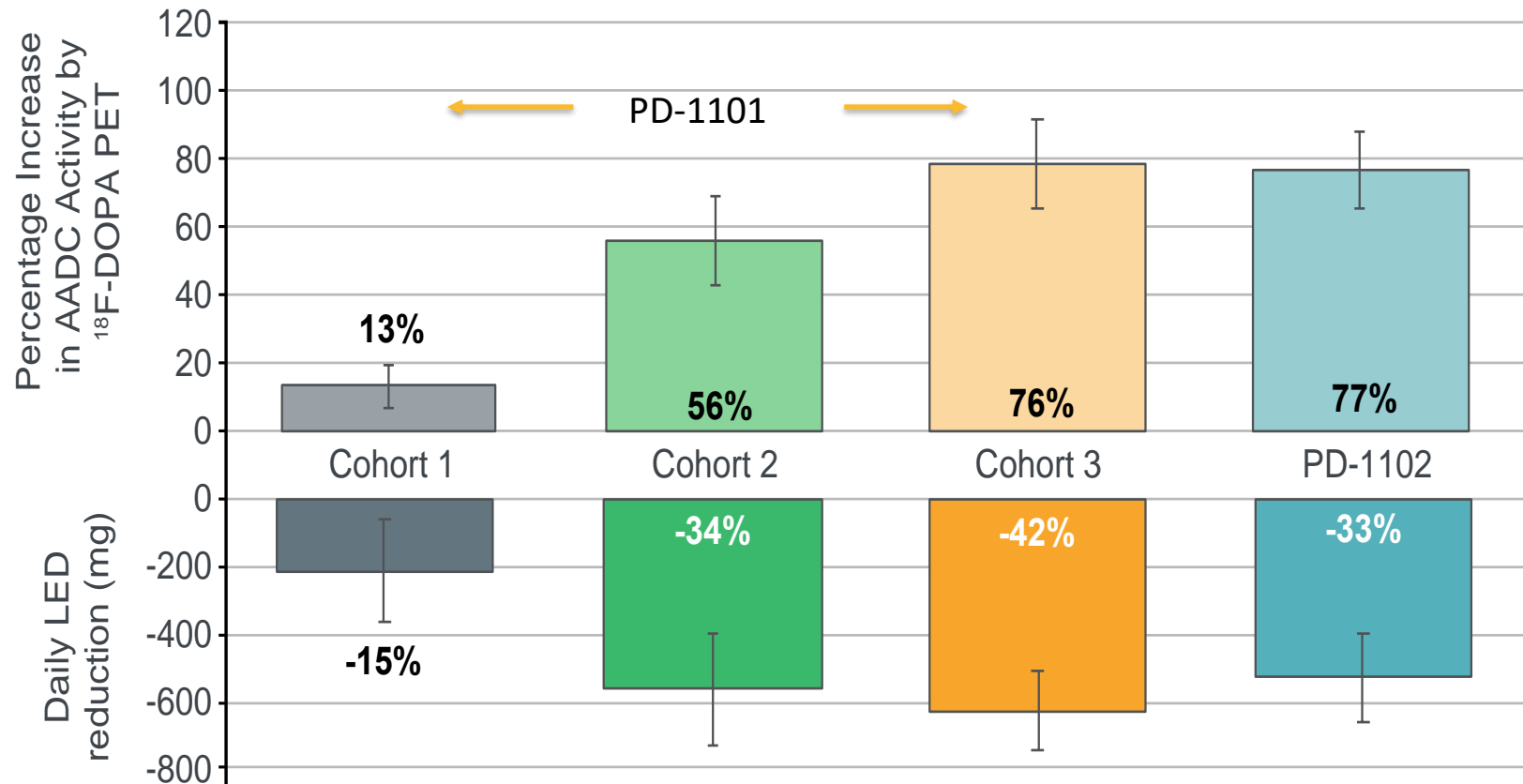
PET, Positron Emission Tomography



Imaging frames captured 65–75 min after <sup>18</sup>F-DOPA administration. <sup>a</sup>Standardized uptake ratios (SORs) were calculated using bilaterally averaged occipital time-activity curve (kBq/mL) region-of-interest values in each subject; <sup>b</sup>data from reference 11.

Source: Poster Presentation, International Parkinson and Movement Disorder Society 2018

# Increases in AADC Activity and Decreases in LED at 6 months



Source: Voyager Therapeutics



# Change in Good ON time and OFF time per 16-hr Waking Day

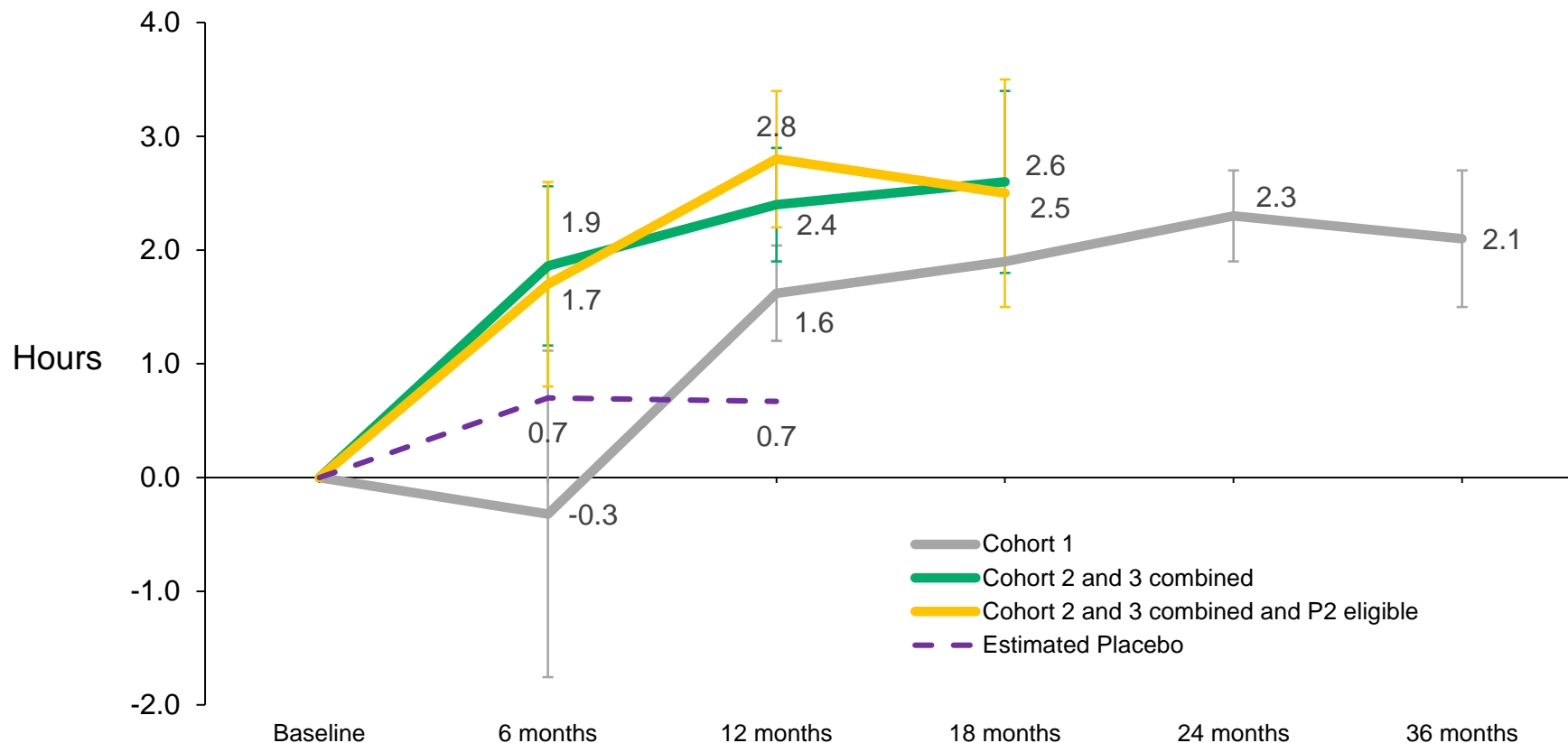
<b>Good ON time: hour improvement from baseline (SE)</b>	<b>Baseline</b>	<b>12-months</b>	<b>18-months</b>	<b>2-years</b>	<b>3-years</b>
Cohort 1, n=5	10.5 (1.0)	1.6 (0.4)	n/a <sup>1</sup>	2.3 (0.4)	2.1 (0.6)
Cohort 2, n=5	10.6 (0.8)	3.3 (0.6)	3.5 (1.1)	2.7 (1.4)	
Cohort 3, n=5	10.3 (0.7)	1.5 (0.5)	1.7 (1.1)		
PD-1102 Post Traj n=8	9.1 (0.5)	1.7 (0.5)			
<b>Cohorts 2-3, n=10</b>	<b>10.5 (0.5)</b>	<b>2.4 (0.5)</b>	<b>2.6 (0.8)</b>		
<b>Cohorts 2-3 w/o severe dyskinesia, n=7</b>	<b>10.1 (0.5)</b>	<b>2.8 (0.6)</b>	<b>2.5 (1.0)</b>		
<b>PD-1102 Post Traj, w/o severe dysk or ICD n=4</b>	<b>8.8 (0.8)</b>	<b>3.2 (0.5)</b>			
<b>OFF time and ON time w/ troublesome dyskinesia hour per day (SE)</b>	<b>Baseline</b>	<b>12-months</b>	<b>Mean % change</b>	<b>18-months</b>	<b>Mean % change</b>
Cohorts 2-3, n=10	5.5 (0.5)	-2.4 (0.5)	-46%	-2.6 (0.8)	-47%
Cohorts 2-3 w/o severe dysk, n=7	5.9 (0.5)	-2.8 (0.6)	-46%	-2.5 (1.0)	-39%
PD-1102 Post Traj w/o dysk or ICD, n=4	7.2 (1.0)	-3.2 (1.0)			

(1) Protocol amended to include 18-month data collection after Cohort 1 reached this timepoint

(2) Mean % change from baseline is calculated as the mean of all individual patient's percent change from baseline

# Durable, Clinically Meaningful Improvements in Good ON Time

*PD-1101: 2.8 hour improvement at 1 year in Cohort 2/3 combined and Phase 2 eligible group (n=7)*

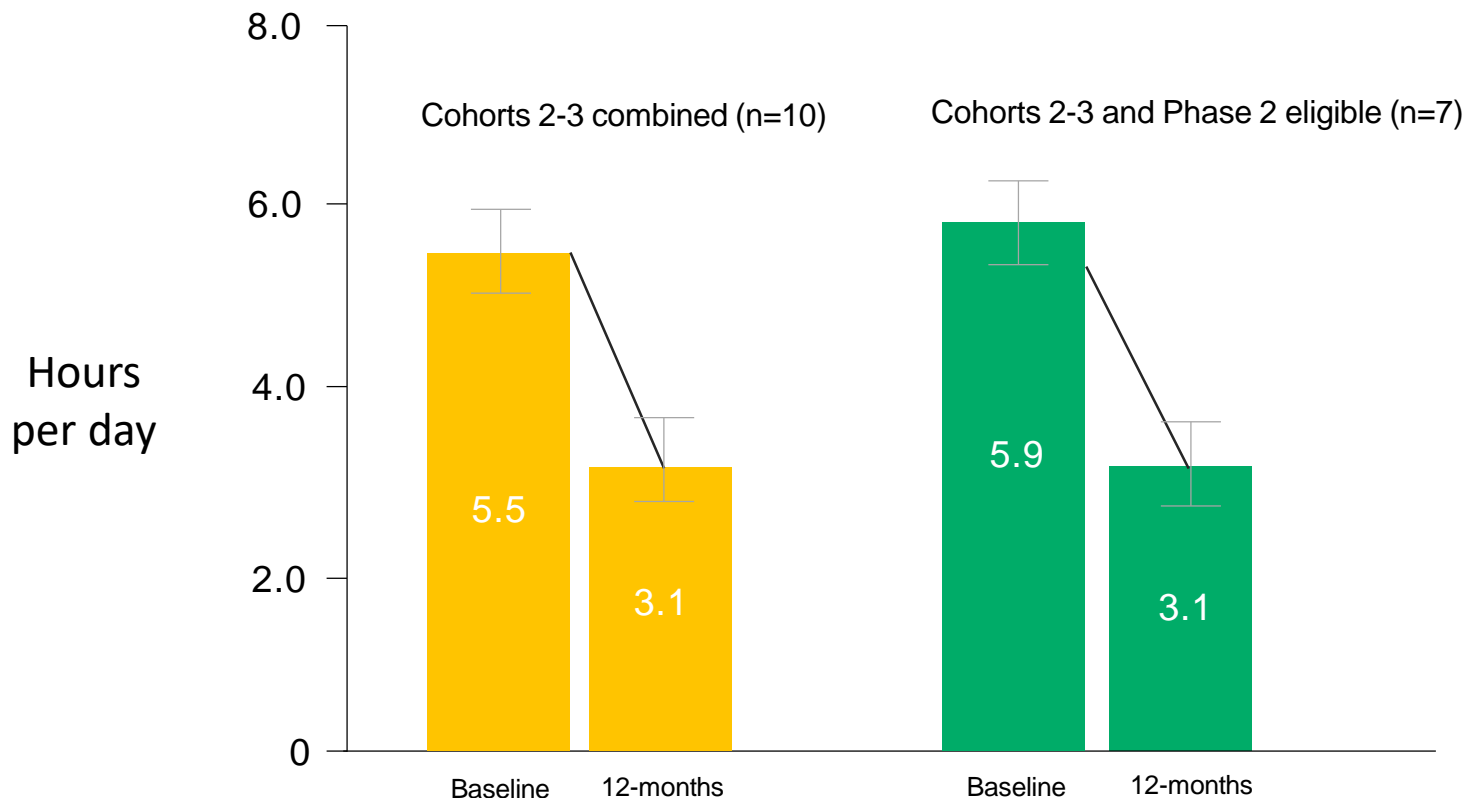


Source: Voyager Therapeutics press release 11/7/18

Note: Estimated placebo data from Marks et al, Lancet Neurol, 2010; Olanow et al, Ann Neurol, 2015

# Durable, Clinically Meaningful Reductions in OFF Time

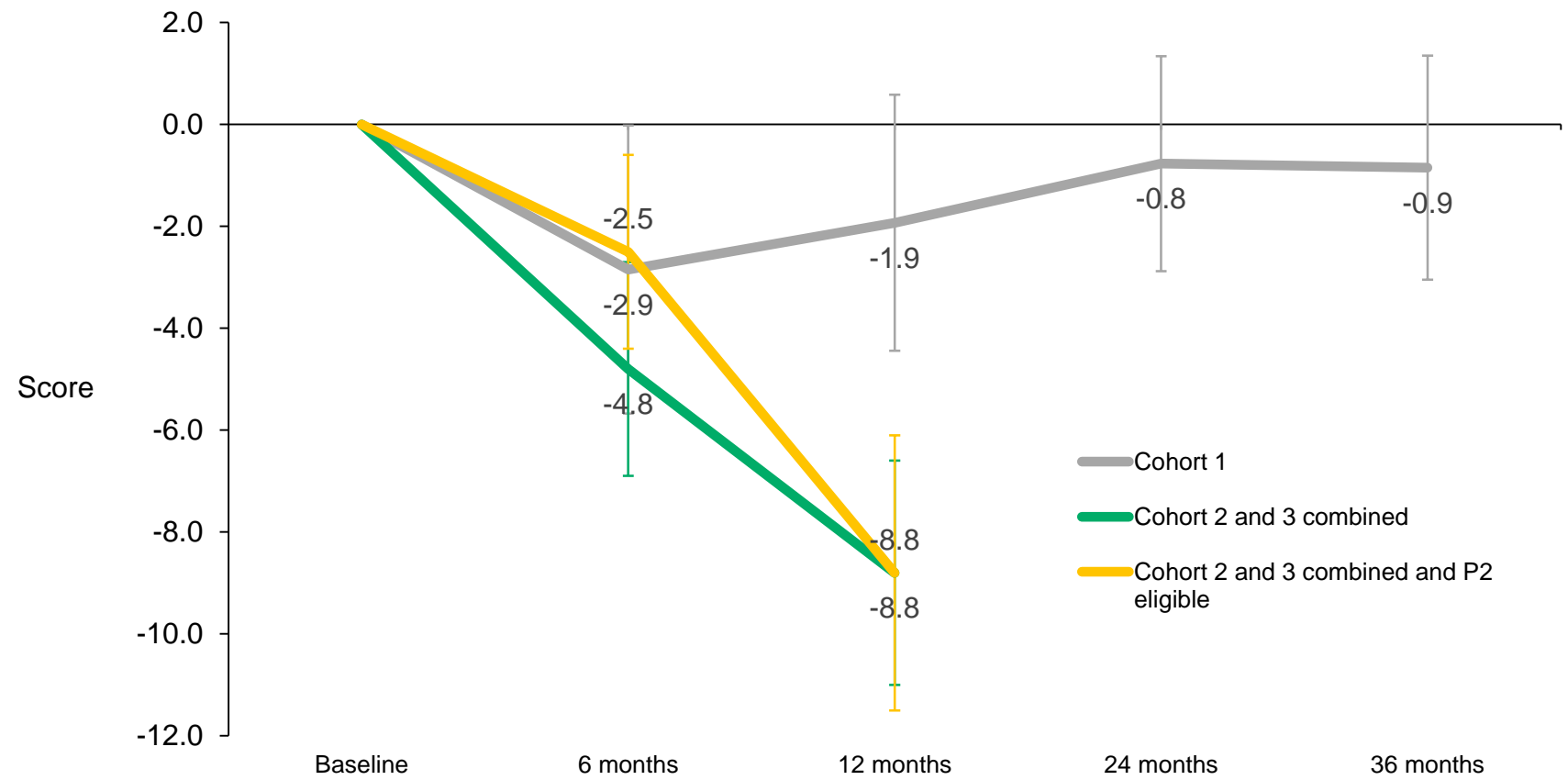
*PD-1101: 46% reduction in OFF time and ON time w/ troublesome dyskinesia at 1 year*



Source: Voyager Therapeutics press release 11/7/18

# Durable, Meaningful Improvements in Quality of Life (PDQ-39)

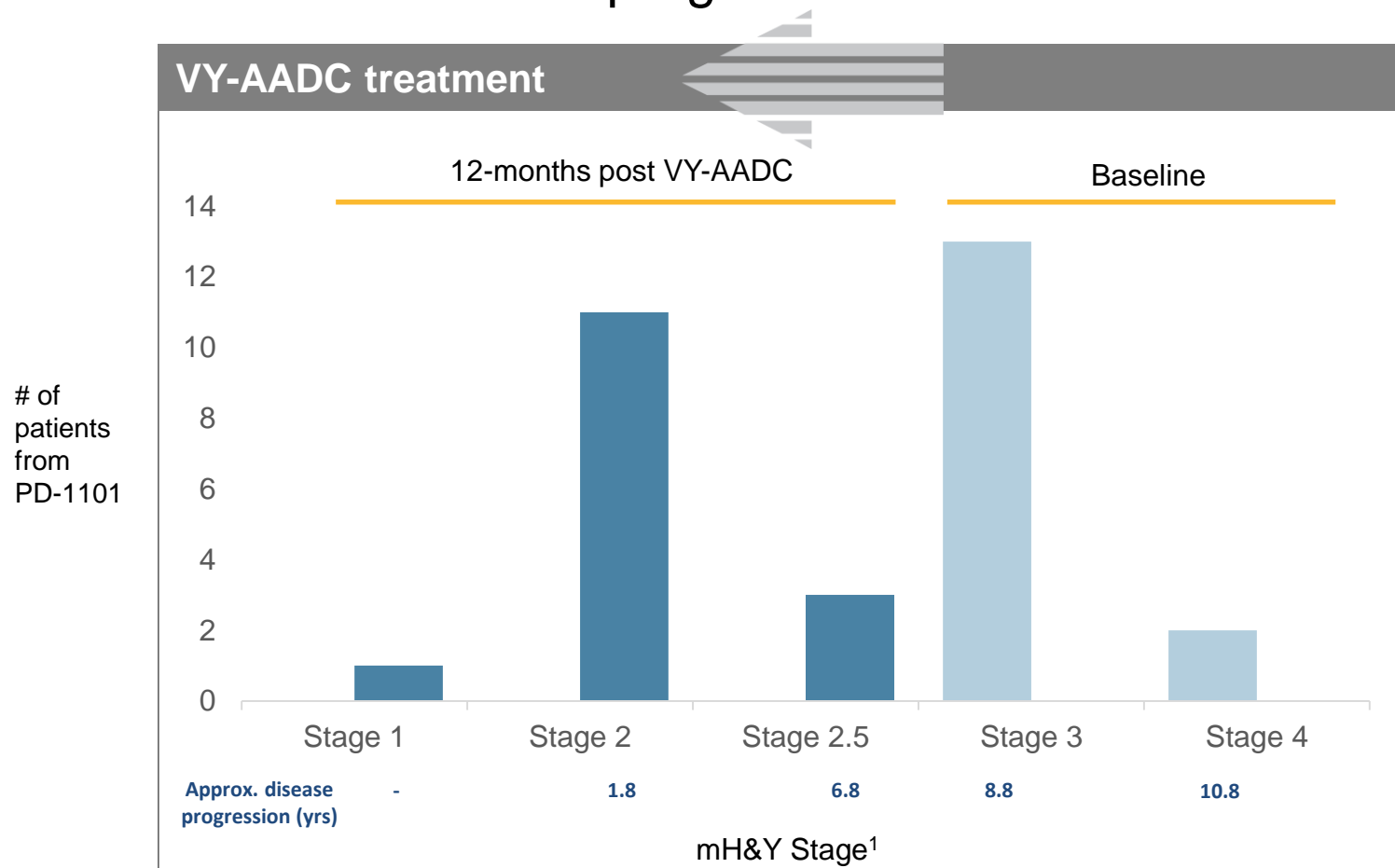
*PD-1101: ~9-point reduction (improvement) in PDQ-39 scores for highest dose Cohorts*



Source: Voyager Therapeutics  
Note: Full Cohort 2 and 3 data at 24 months not yet available

# Marked Shift in mH&Y Disease Staging at 12 months

Observed shift in disease progression based on mH&Y stages<sup>1</sup>



- (1) mH&Y= modified Hoehn and Yahr scale. Shift assessment based on median time to transit per Stage from Zhao et al, Mov Disord. 2013. Stage 1=unilateral disease, Stage 2= bilateral disease w/o impairment of balance, Stage 2.5=mild bilateral disease, with recovery on pull test, Stage 3= mild to moderate bilateral disease; some postural instability; physically independent, Stage 4=severe disability; still able to walk or stand unassisted.



# Significant Reductions in Levodopa-Equivalent Doses

*PD-1101: Improvements in ON and OFF Time and PDQ-39 scores achieved with dramatic reductions in LED doses at higher dose Cohorts*

- 43% reduction for Cohort 3 at 18-months
- 21% reduction for Cohort 2 at 2 years
- 15% increase for Cohort 1 at 3 years <sup>1</sup>

(1) LEDs increased to above baseline in Cohort 1 at 3 years due to a single patient

# VY-AADC Phase 1b (PD-1101) Results: Safety

- Surgical procedure successfully completed in all 15 patients.
- Infusions of VY-AADC01 have been well-tolerated with no vector-related serious adverse events (SAEs).
- 14 of the 15 patients were discharged from the hospital within two days following surgery.
- As previously reported, one patient experienced two SAEs - a pulmonary embolism, or blood clot in the lung, and related heart arrhythmia, or irregular heartbeat.
  - Patient treated with an anti-coagulant and symptoms associated with the SAEs have completely resolved.
  - Investigators determined that this was most likely related to immobility during the surgical procedure and subsequent formation of a blood clot, or deep vein thrombosis (DVT), in the lower extremity. Consequently, DVT prophylaxis was added to the surgical protocol and no subsequent events have been observed following implementation of these measures.

# Posterior Trajectory Phase 1 Trial (PD-1102)

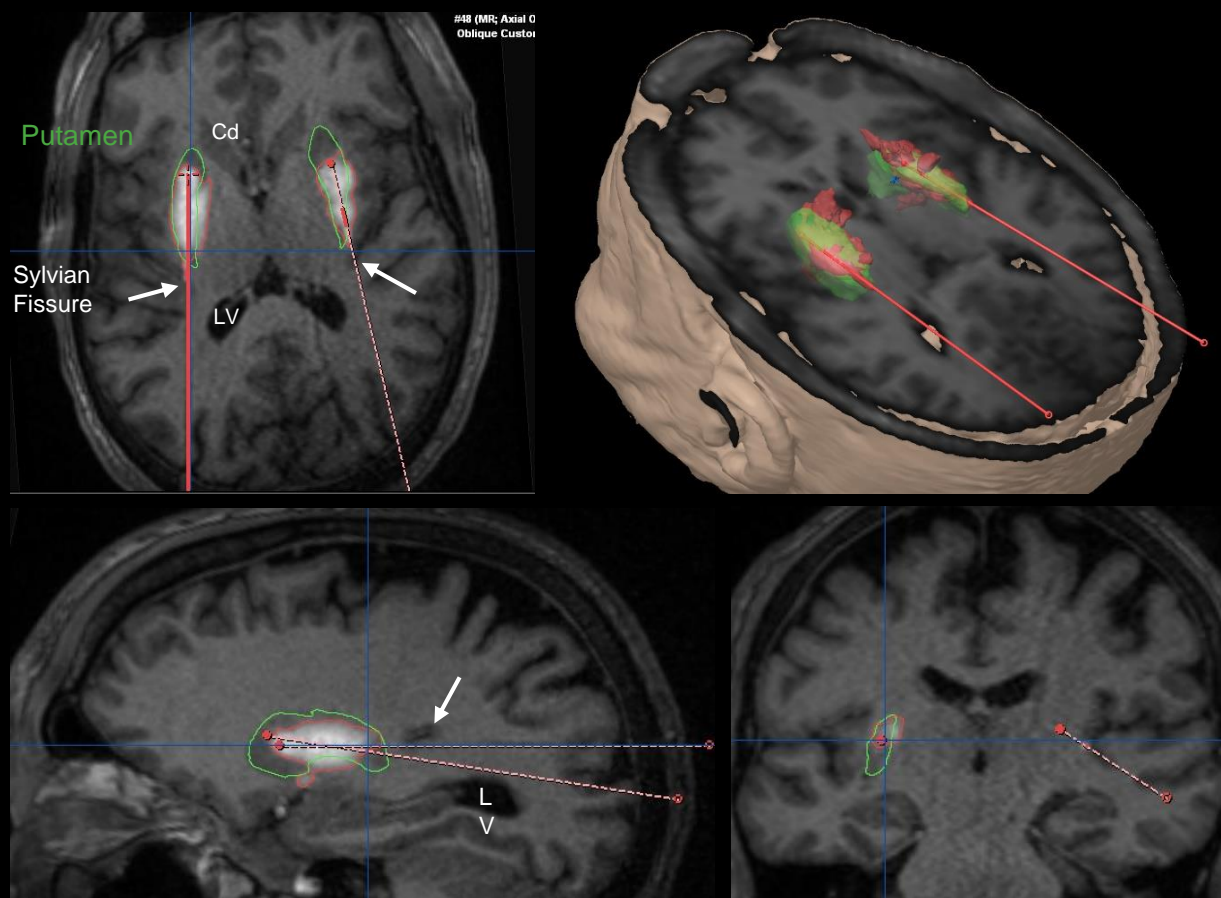
- Completed dosing in 8 patients
- 54% average putaminal coverage
- Reduced infusion time by two hours (from five hours to three hours) compared with PD-1101
- Confirmed the findings from PD-1101 that VY-AADC leads to increases in AADC enzyme activity and improvements in motor function and quality of life in patients with Parkinson's disease – with less need for oral levodopa medication
- Well-tolerated, no serious adverse events



Source: 2019 American Academy of Neurology Annual Meeting Van Laar poster presentation

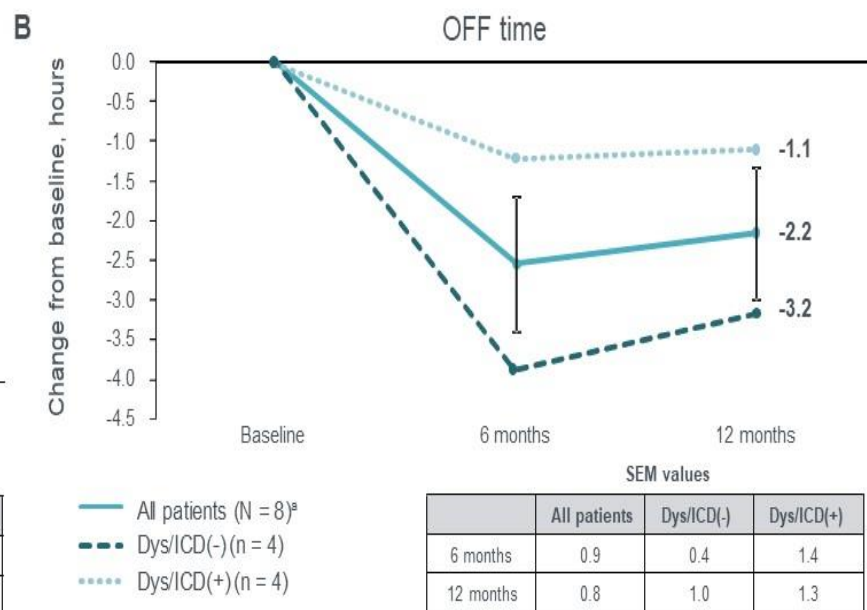
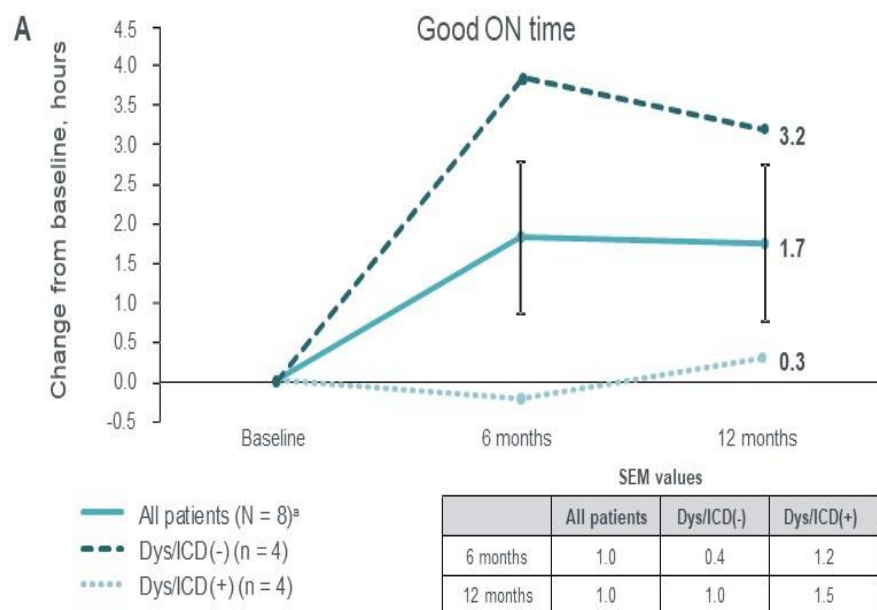
# Posterior Trajectory Overview

- Single trajectory per putamen → Reduced Infusion Time
  - Increased Putamen Coverage



# PD-1102 Good ON time and OFF time Results

Change from baseline in diary (A) Good ON and (B) OFF time normalized to 16-hour waking day



<sup>a</sup>Excluding patient who received lower vg concentration, change in good ON time  $1.4 \pm 1.1$  hours and OFF time  $-1.9 \pm 0.9$  hours at 12 months.  
 Dys/ICD(-), no or low baseline dyskinesia and absence of ICD at baseline; Dys/ICD(+), high baseline dyskinesia or ICD at baseline

Source: 2019 American Academy of Neurology Annual Meeting Van Laar poster presentation

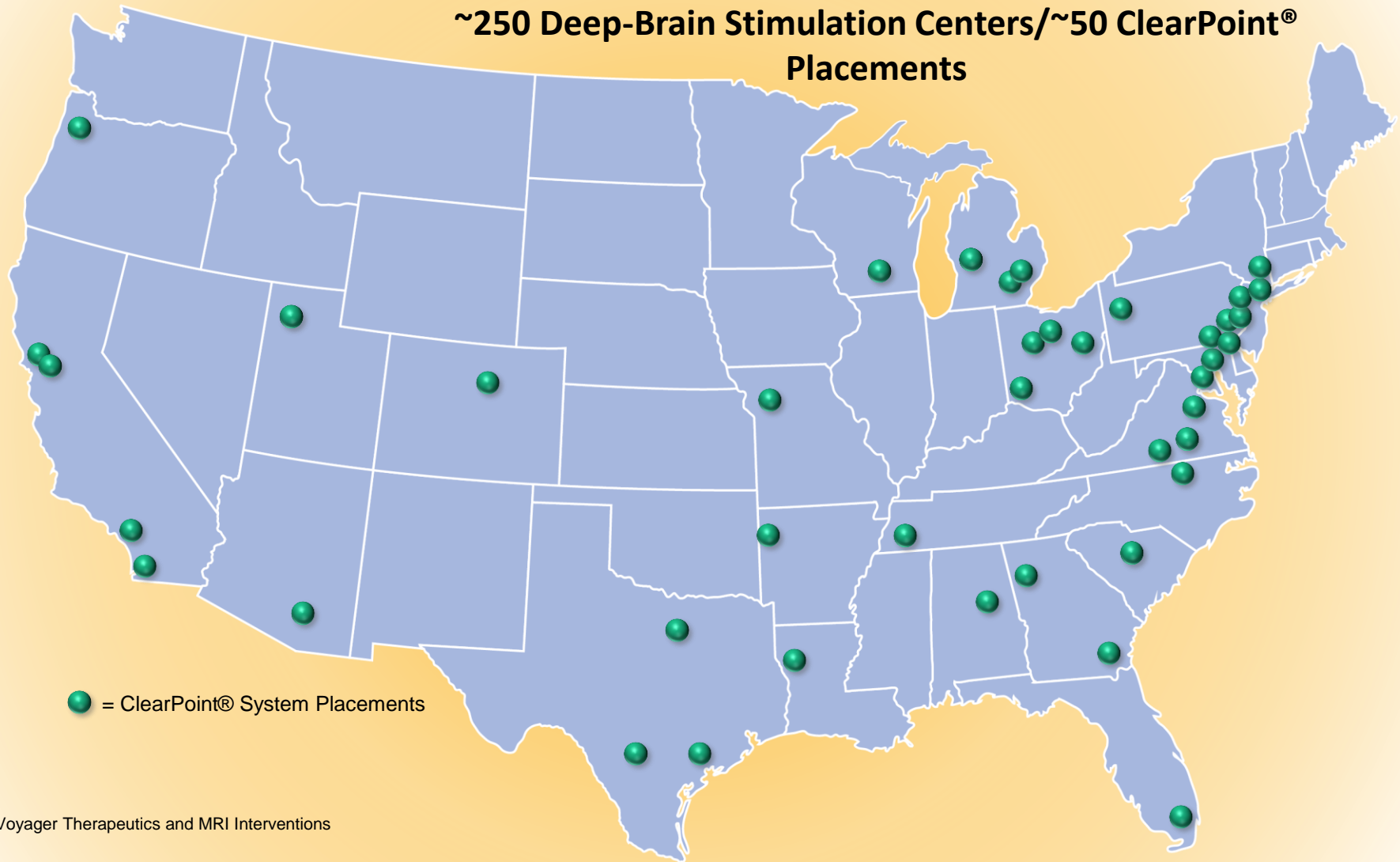


# RESTORE-1,-2: Phase 2-3 trials of VY-AADC

RESTORE-1 and -2: Randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of VY-AADC for the treatment of Parkinson's disease in 75-100 patients (each trial) with motor fluctuations that are refractory to medical management

- **Population:** PD diagnosis  $\geq 4$  yrs, are not responding adequately to oral medications, and have  $\geq 3$  hours of OFF time. Randomized (1:1) to one-time administration of VY-AADC (for a total dose of up to  $2.5 \times 10^{12}$  vector genomes) or placebo surgery.
- **Primary endpoint:** ON time without troublesome dyskinesia, or good ON time, as measured by a self-reported patient diary at 12 months.
  - Secondary endpoints include diary OFF time, other motor function and quality of life measures from the United Parkinson's Disease Rating Scales (UPDRS-II,-III scores), the Parkinson's Disease Questionnaire (PDQ-39), and patient's global function as measured by the proportion of participants with improvement on the Clinical Global Impression (CGI) score. The trial will also measure non-motor symptoms from the Non-Motor Symptom Scale (NMSS), as well as safety.
- **Biomarker data:** VY-AADC putaminal coverage, AADC enzyme expression and activity by PET using fluorodopa F-18, and changes in patients' daily doses of oral levodopa.

# Focusing on DBS Centers and Centers of Excellence



Source: Voyager Therapeutics and MRI Interventions



# Huntington's Disease

## ALS (SOD1)

## Friedreich's Ataxia



# Huntington's Disease Program Overview

~70,000 Prevalence (U.S./EU)

- Progressive decline of motor and cognitive functions; symptoms occur during ages of 30 to 50 and worsen over a 10 to 25-year period
- Toxic gain-of-function mutation in the *huntingtin*, or HTT, gene (CAG expansion) leads to abnormal intracellular huntingtin protein aggregates causing neuronal cell death
- VY-HTT01: anti-HTT RNAi gene trx to knockdown HTT mRNA in striatum and cortex to slow disease progression



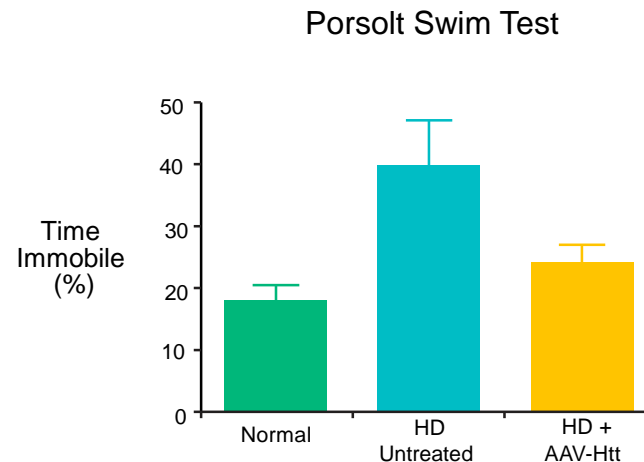
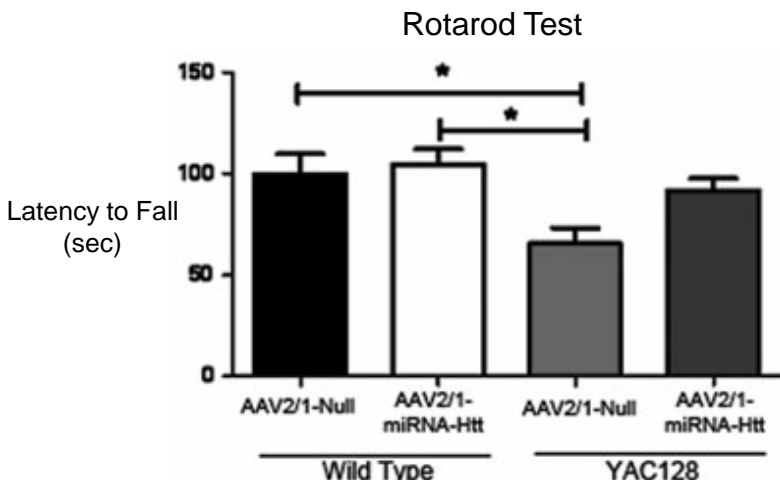
# AAV Gene Therapy Rationale for Lowering HTT

- Mutant huntingtin is causal for disease and has numerous deleterious molecular and cellular effects
- Transgenic models confirm pathogenicity of poly-Q HTT
- RNAi or ASO studies in HD animal models demonstrate that partial lowering of HTT provides potential therapeutic benefit and is well-tolerated

*> 40% knockdown of HTT results in significant functional benefit*

~55% Knockdown of HTT with AAV Ameliorates Rotarod Deficits in Mouse Model (YAC128)

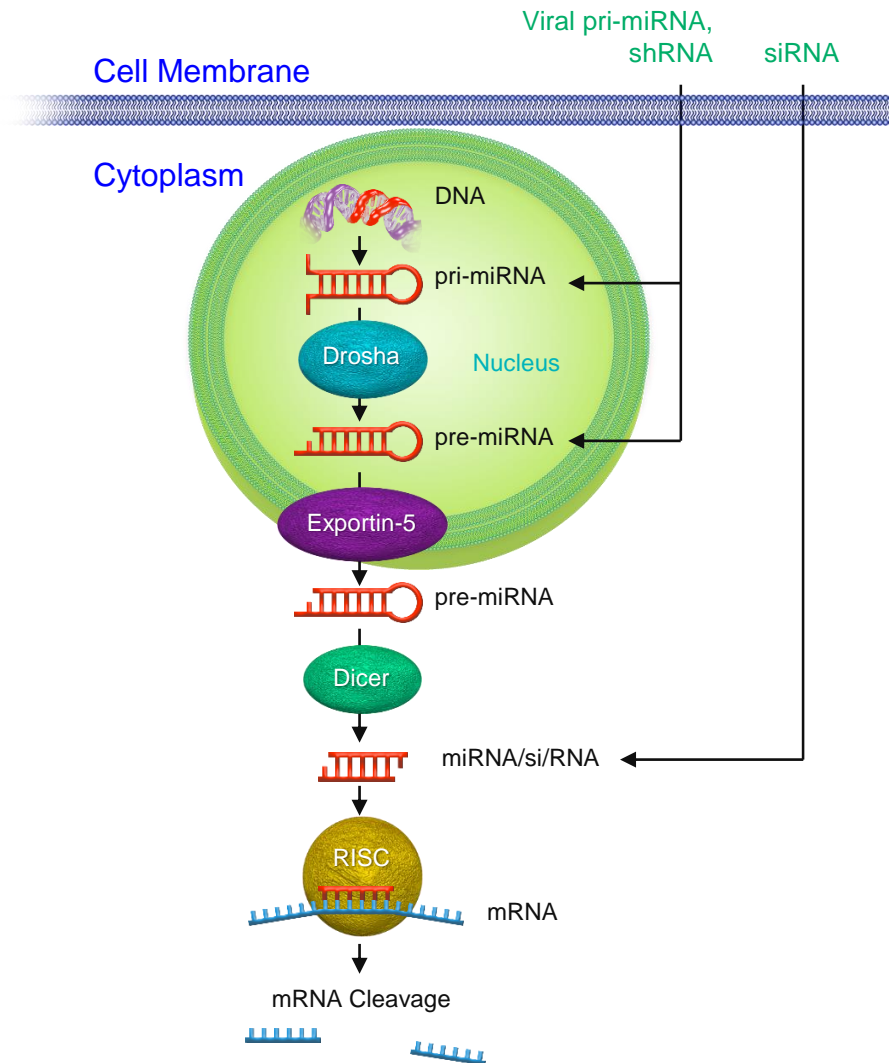
~55% Knockdown of HTT with AAV Normalizes Depressive Behavior in Mouse Model (YAC128)



Source: Stanek et al., 2014

# RNAi Mechanism of an HTT-Lowering AAV Gene Trx

- ❖ Pri-miRNA (with flanking regions) or pre-mRNA/shRNA (no flanking regions) are virally delivered (e.g. by AAV)
- ❖ Expressed pri-miRNA or pre-miRNA are processed by the cell's endogenous pathway to a miRNA duplex
- ❖ miRNA duplex unwinds, binds to its complementary HTT mRNA substrate, and recruits the RNA-Induced Silencing Complex (RISC)
- ❖ Ago2 in RISC cleaves the target HTT mRNA substrate

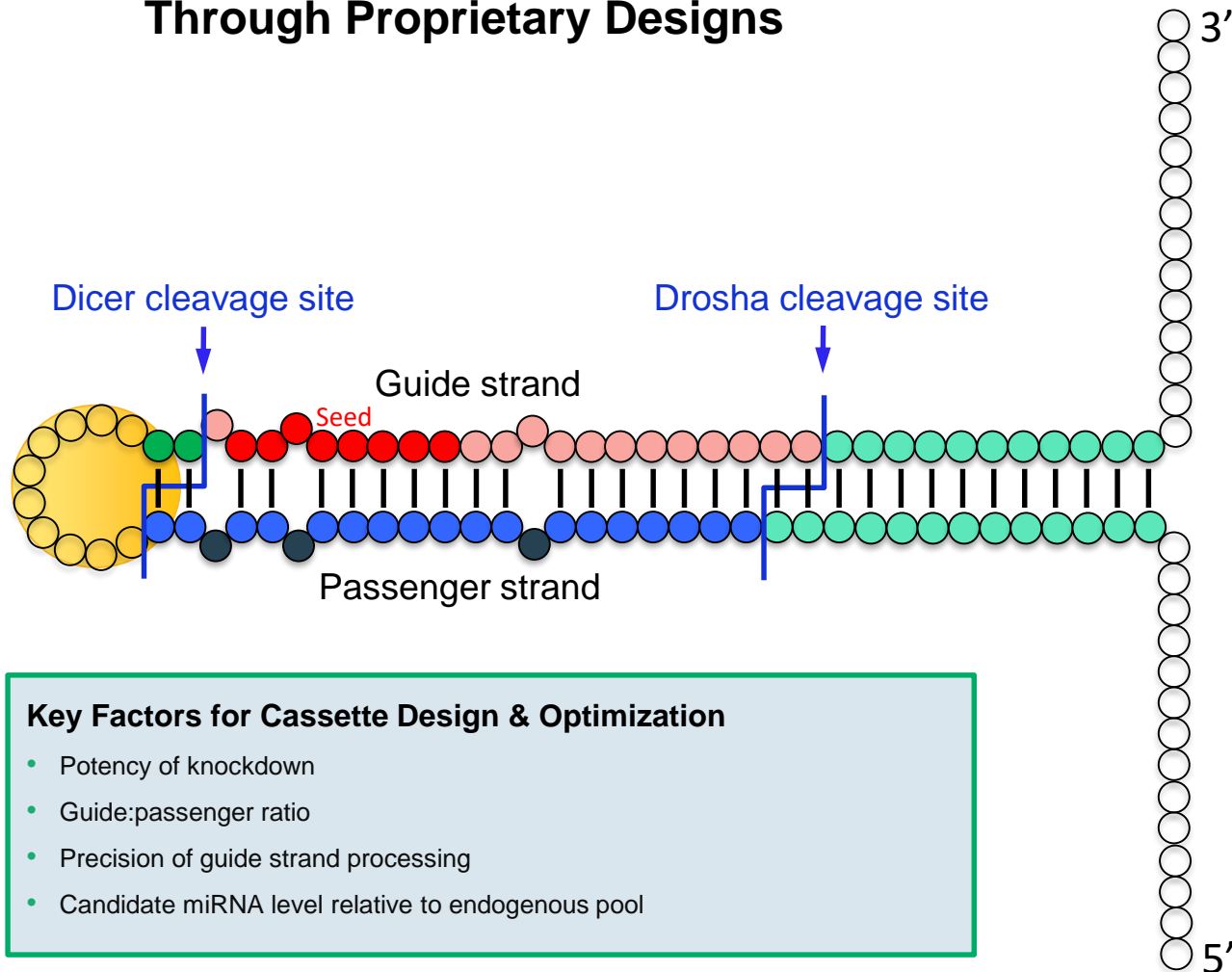


Adapted from Sah and Aronin (2011) JCI



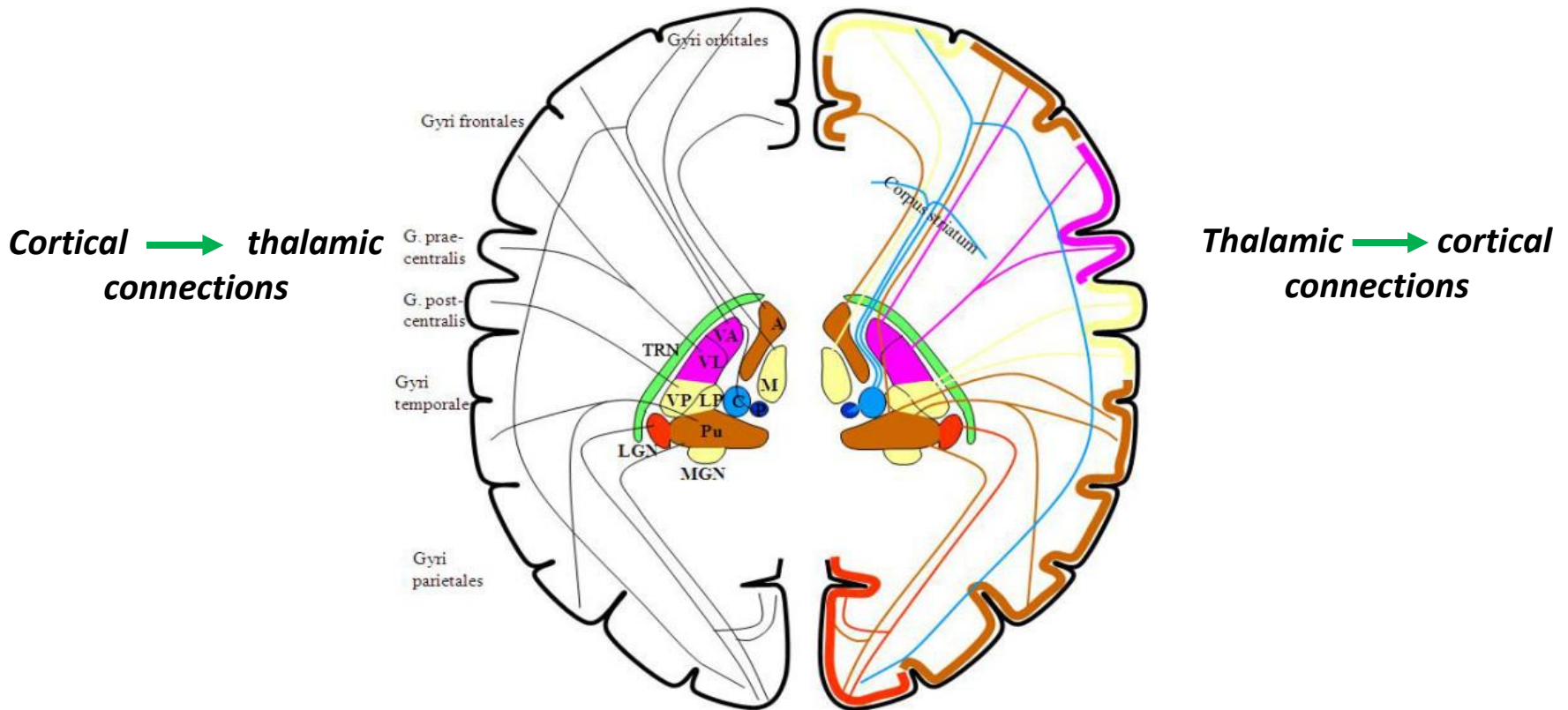
# Gene Therapy Cassette Design and Optimization

## Platform for Potent and Selective pri-miRNA Discovery Through Proprietary Designs



# Putamen and Thalamus Route of Delivery

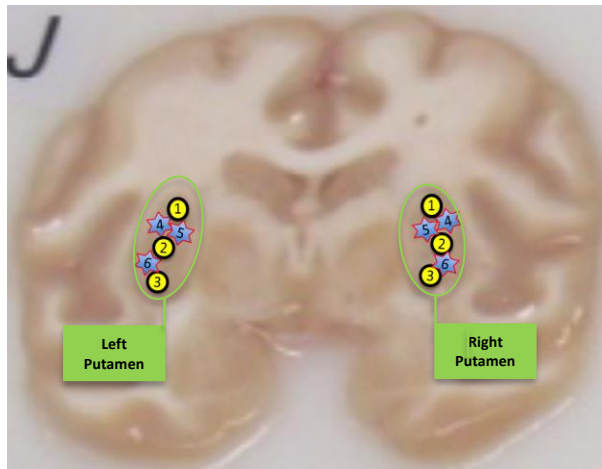
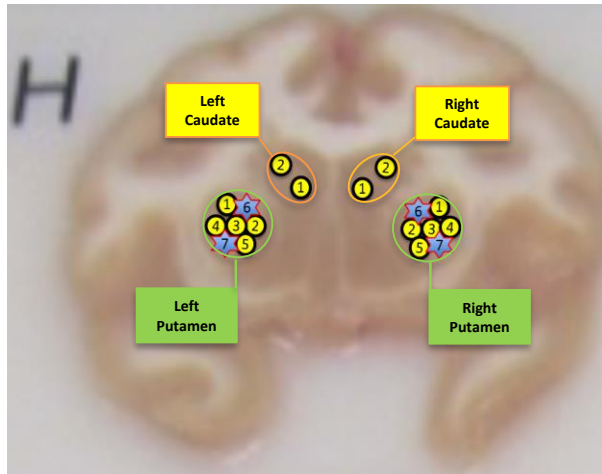
**Putamen-Thalamus leverages more extensive and preserved neuronal pathways to the cortex than delivery to the putamen alone**



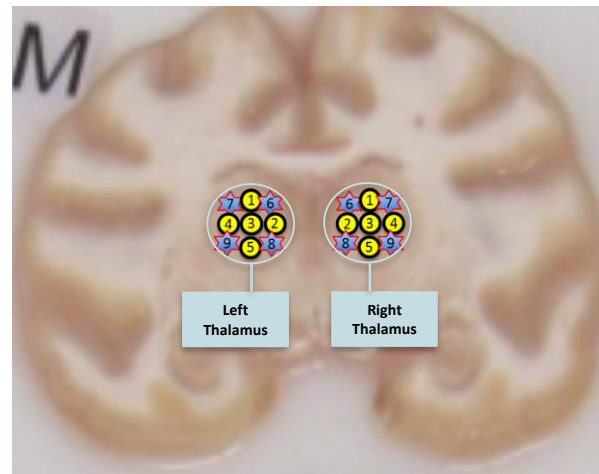
Source: Min 2010, Theor Biol Med Model

# Brain Tissue Punch and Laser-Capture Locations

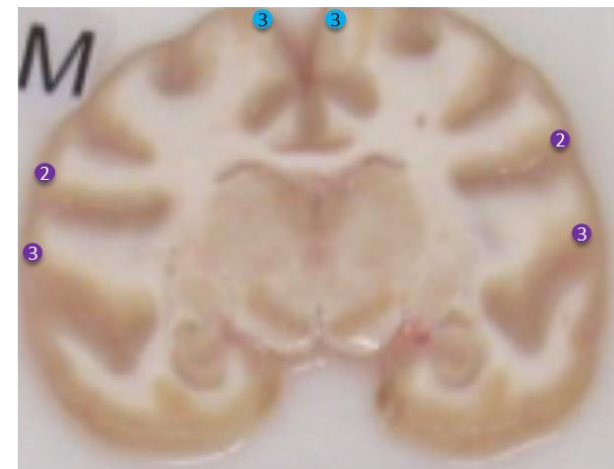
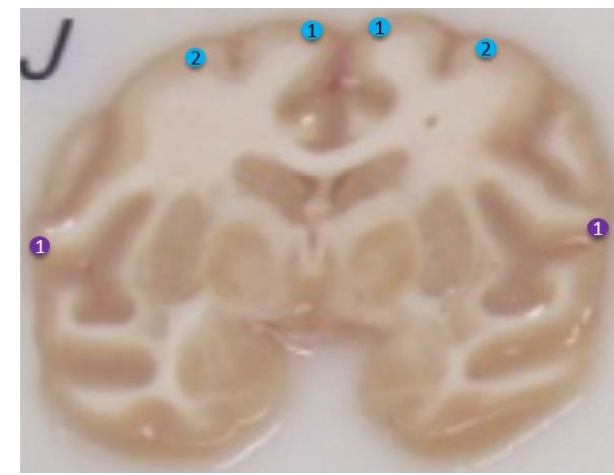
## Striatum (Putamen and Caudate)



## Thalamus



## Cortex (Laser Captured Neurons)



- 2 mm punch for VG, mRNA
- 3 mm punch for protein
- 2mm *motor cortex* punch
- 2mm *somatosensory cortex* punch

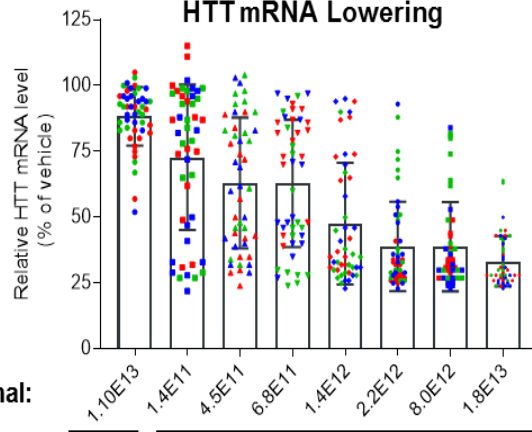
Source: ESGCT 2018 Poster P190

# Robust HTT mRNA Lowering in Adult NHPs

## Putamen (67%), Caudate (68%), and Cortical Neuron (32%) HTT mRNA Lowering<sup>1</sup>

### Putamen

#### HTT mRNA Lowering

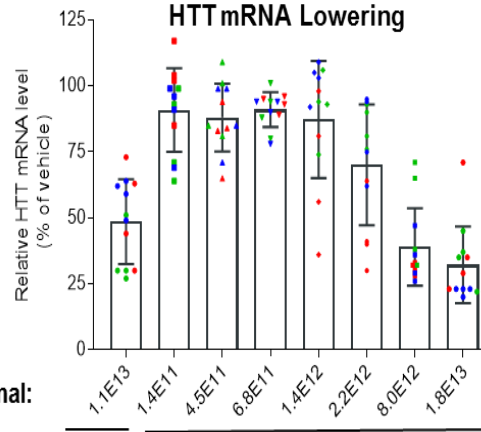


VG/Animal:

Dose Route: Thalamus Putamen + Thalamus

### Caudate

#### HTT mRNA Lowering

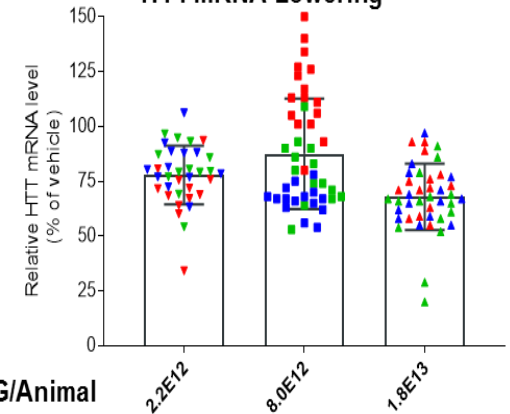


VG/Animal:

Dose Route: Thalamus Putamen + Thalamus

### Cortical Neurons

#### HTT mRNA Lowering



VG/Animal

Dose route: Putamen + thalamus

Source: ASGCT 2019

(1) HTT mRNA lowering reported from high-dose



# Monogenic ALS Program Overview

ALS Prevalence: ~20,000 (U.S.) /  
~55,000 (ROW)

- SOD-1 Prevalence: ~800 (U.S.)  
/ ~1,500 (ROW)

- Rapidly progressive neurodegenerative disease with adult-onset resulting in severe muscle atrophy; usually fatal within 2-4 years of diagnosis
- Toxic gain-of-function mutation in superoxide dismutase 1 (SOD1) gene causes ~15-20% of familial cases and ~1-2% of sporadic cases WW
- VY-SOD101: anti-SOD1 RNAi gene therapy directly to the CNS to knockdown SOD1 mRNA to slow the progression of disease



# Preclinical Data Supports AAV Gene Therapy Lowering SOD1 for ALS

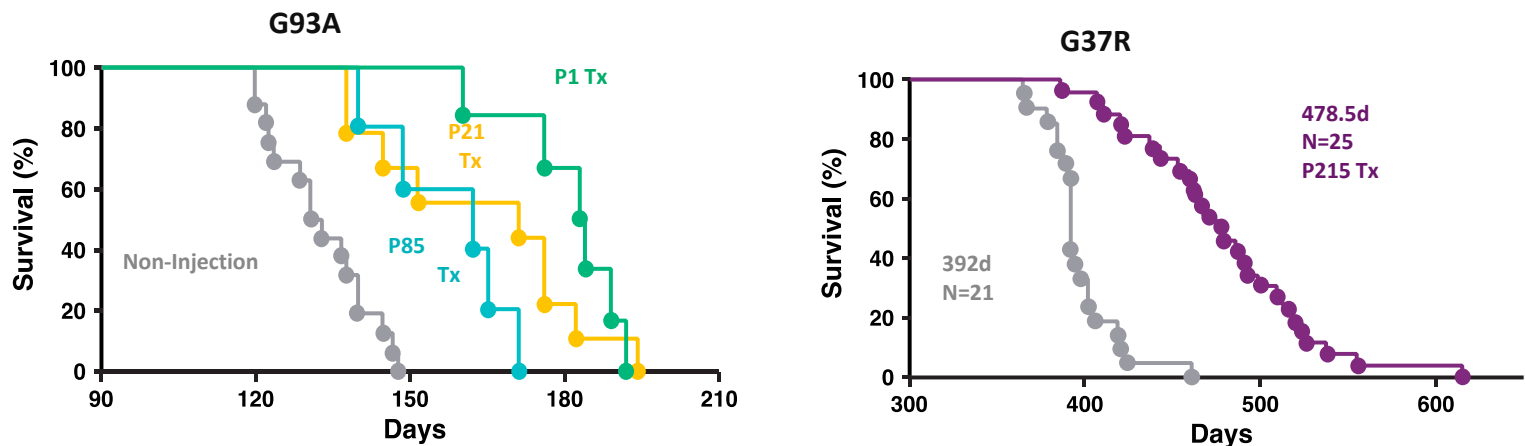
## Mutant SOD1 is associated with disease:

Mutant SOD1 forms toxic aggregates resulting in dysfunction/degeneration of motor neurons

## Lowering mutant SOD1 provides therapeutic benefit:

Lowering SOD1 with RNAi/ASO extends survival and improves motor function in ALS mouse models

### *IV AAV9-shSOD1 Extends Survival of ALS Mouse Model*

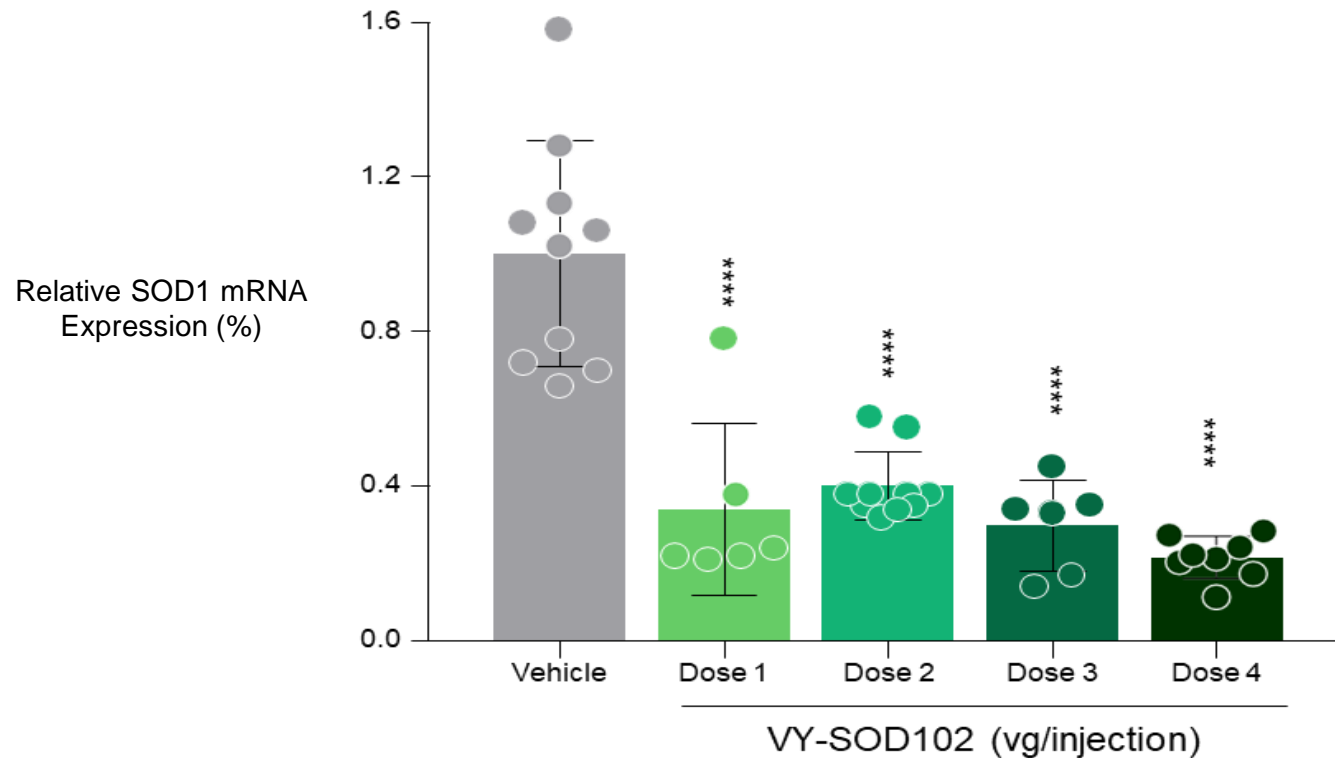


Source: Foust et al., 2013



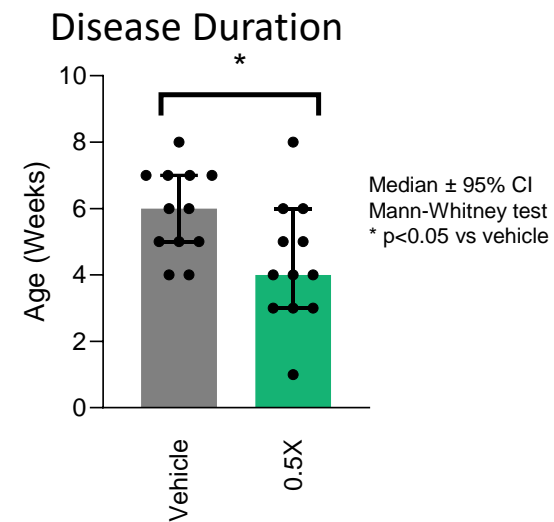
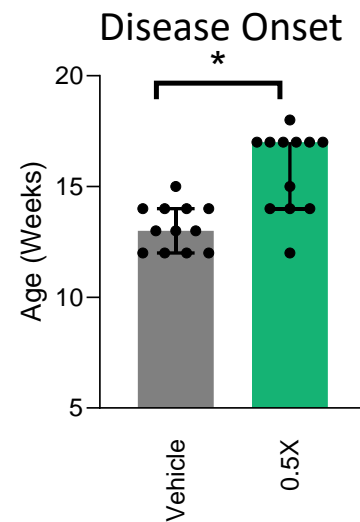
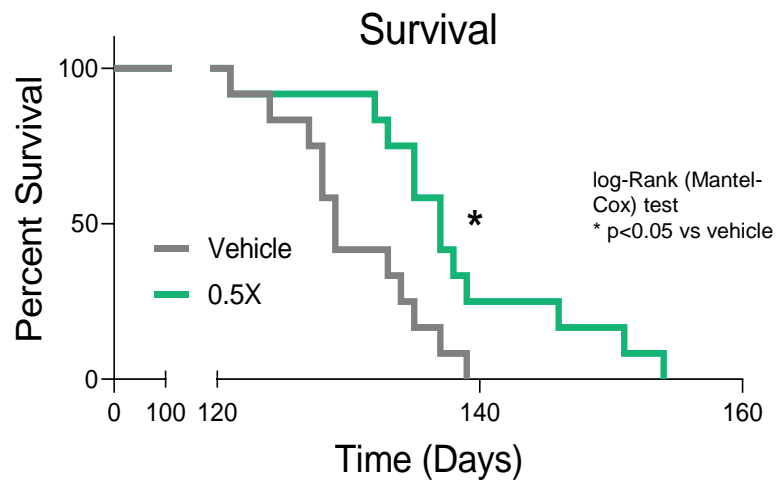
# VY-SOD102: Robust Reduction of Human SOD1 in Transgenic Mice

**Significant mRNA SOD1 reduction 4-weeks post intrastriatal dosing**



Source: ESGCT 2018 Poster P185

# VY-SOD102: Improvement of Disease Course and Survival in G93A Mouse Model of ALS-SOD1



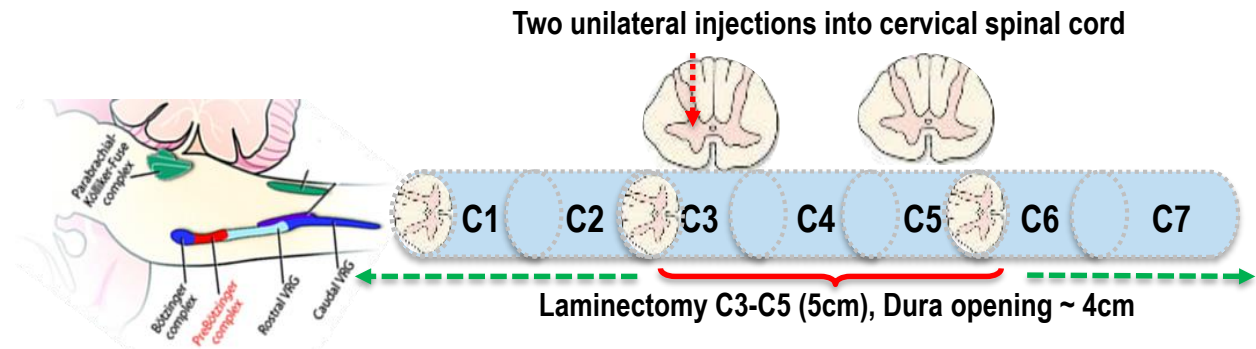
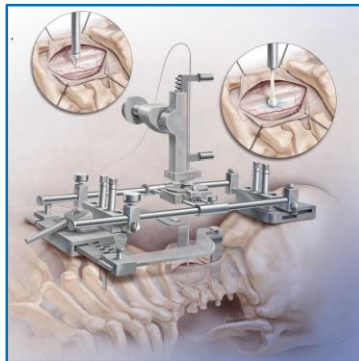
Source: ASGCT 2019  
Bilateral intra-lumbar spinal cord delivery

# VY-SOD102: Novel Delivery Paradigm

## One-time, intraparenchymal infusion after laminectomy to the cervical spinal cord of the Gottingen mini-pig:

Spinal cord similar in length and diameter to the human spinal cord

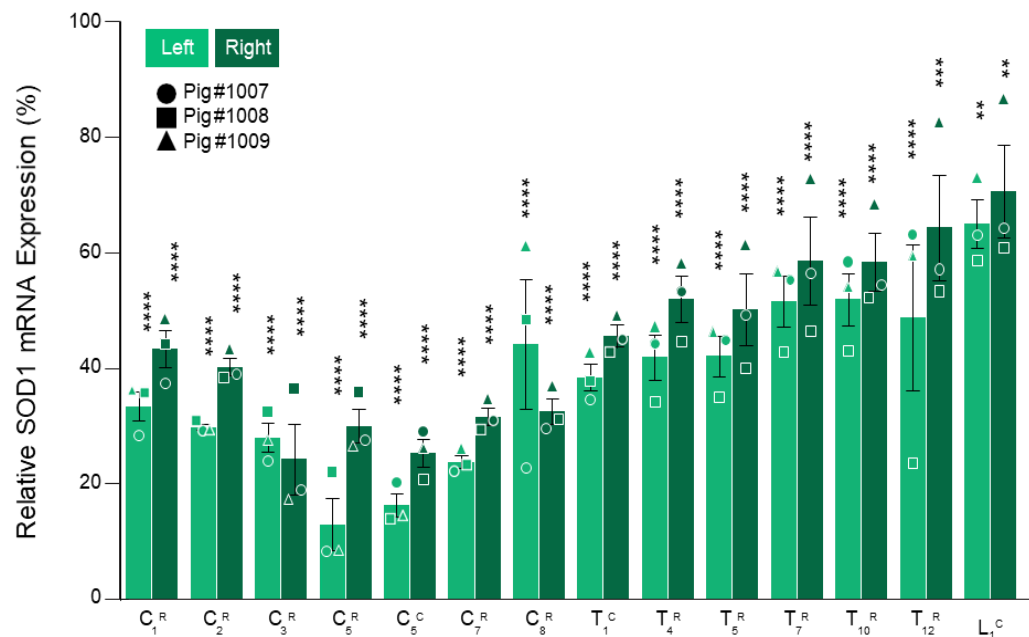
Site of infusion (C3-C5) aligns with respiratory failure as most common cause of mortality



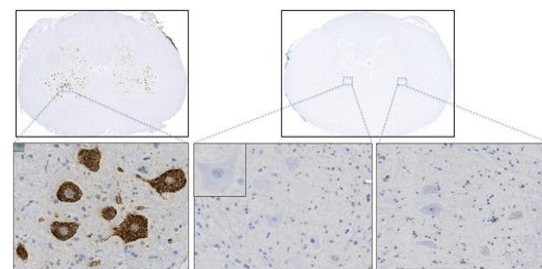
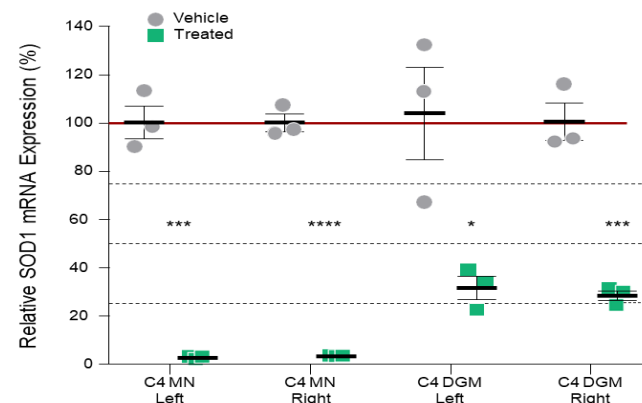
Source: ESGCT 2018 Poster P185

# Robust SOD1 mRNA Reduction in Pig Spinal Cord

**70%, 50% and 22% SOD1 mRNA reduction in the cervical, thoracic and lumbar regions:**



**82% SOD1 mRNA reduction near site of cervical injection:**



Vehicle

VY-SOD102

Source: ESGCT 2018 Poster P185

# Friedreich's Ataxia Program Overview

## 17,000 Prevalence (U.S./EU)

- Fatal, debilitating neurodegenerative and cardiac disease.
- Typical age of onset is 10 to 12 years and life expectancy is severely reduced due to neurological and cardiac complications between 35 to 45 years of age
- Mutations of frataxin (FXN) gene reduce production of frataxin protein resulting in degeneration of sensory pathways and debilitating symptoms
- Gene therapy to restore FXN protein levels to at least 50% of normal in relevant neurons and cardiac myocytes to slow the progression of disease





# Friedreich's Ataxia (FA)

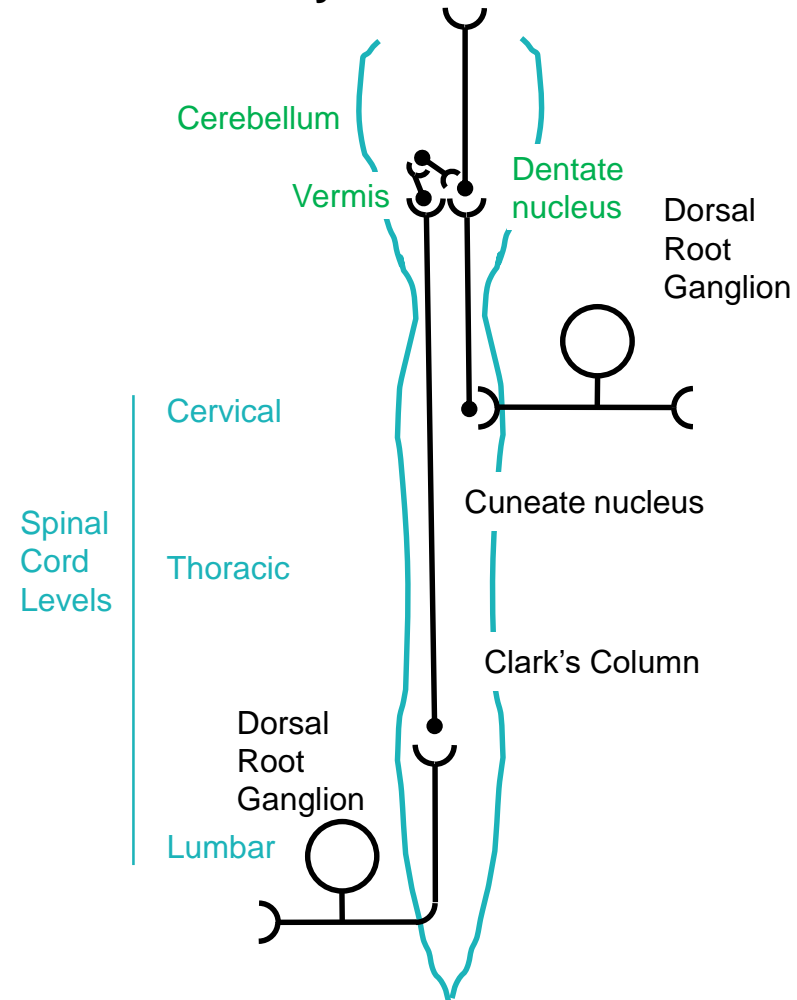
**Fatal, debilitating neurodegenerative and cardiac disease affecting ~6,400 patients in the US:**

- Progressive ataxia to wheelchair dependence, loss of sensation, cardiomyopathy, scoliosis and diabetes as well as impaired vision, hearing and speech
- Typical age of onset is 10 to 12 years of age, and life expectancy is severely reduced with death from neurological and cardiac complications between 35 to 45 years of age
- Autosomal recessive disorder - mutations of frataxin (FXN) gene reduce production of frataxin protein resulting in degeneration of sensory pathways and debilitating symptoms

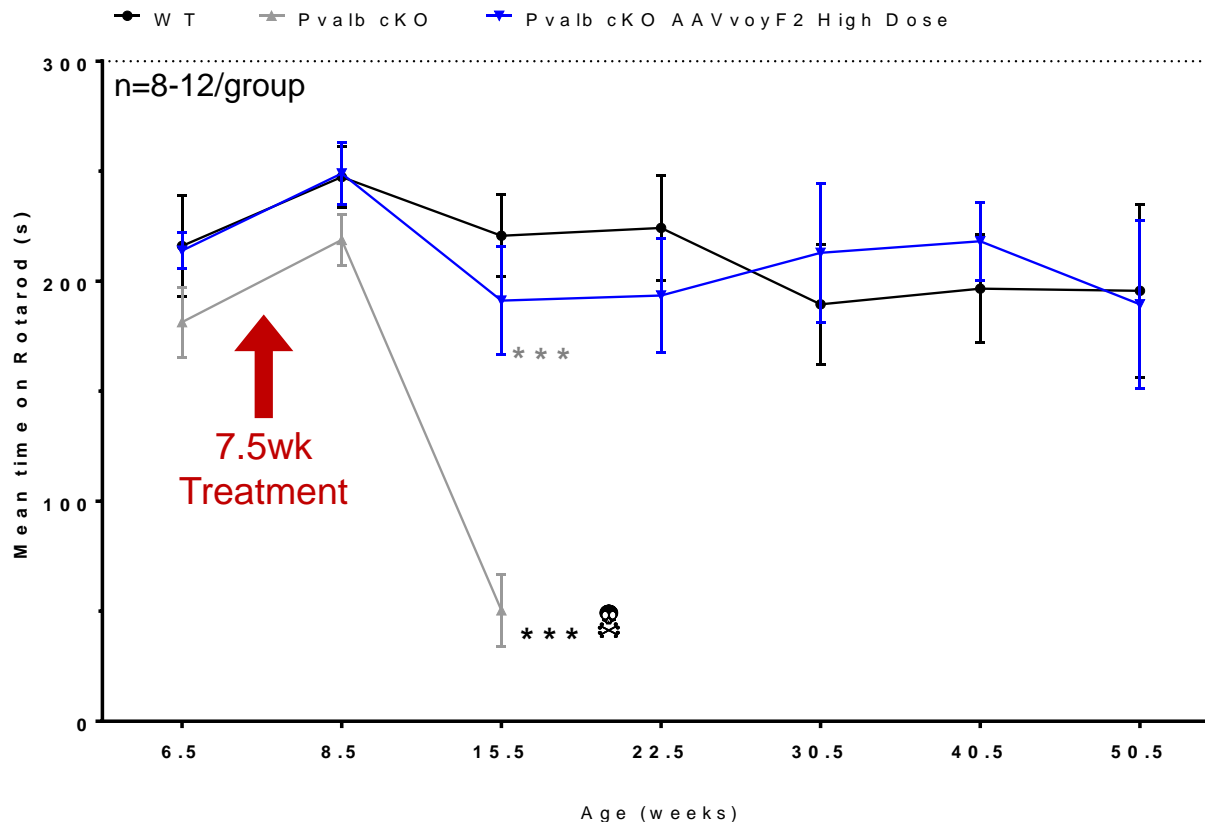
## Goal

- Develop an AAV gene therapy for the treatment of FA by restoring FXN protein levels to slow the progression of disease

## Ascending Sensory Pathways to the cerebellum



# Long-Term Prevention of Rotarod Deficit by IV AAVvoyF2-cFXN-HA



- Long-term prevention of rotarod deficit maintained for 10 months after IV treatment of Pvalb cKO mice with high dose AAVvoyF2-cFXN-HA

# Vectorized Antibody Approach Targeting:

- *Tau* for Alzheimer's disease and other tauopathies
- *Alpha-synuclein* for Parkinson's disease and other synucleinopathies

# AbbVie Collaboration Targeting Tau: Overview and Goal

## Overview:

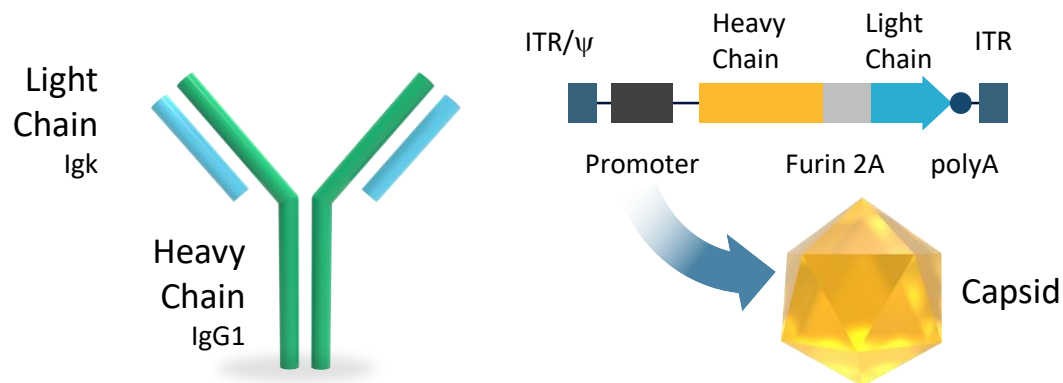
- In tauopathies, tau aggregates and becomes hyper-phosphorylated, forming insoluble tau-containing neurofibrillary tangles
- The progressive spread of tau pathology along distinct anatomical pathways in the brain closely correlates with disease progression and severity in a number of tauopathies, including Alzheimer's disease, frontotemporal lobar degeneration (FTD), Pick's disease, progressive supranuclear palsy (PSP), and corticobasal degeneration
- Attempts to prevent, reduce, or slow the development of tau pathology have become prominent therapeutic strategies for AD and related tauopathies
- Only very low levels of anti-tau monoclonal antibody may reach the brain parenchyma from the systemic circulation

## Goal:

- *Deliver a one-time administration of a vectorized monoclonal antibody directed against tau to potentially treat primary and secondary tauopathies including Alzheimer's disease*

# Vectorized Anti-Tau Antibody Components

## Vectorized Tau Antibody: Example



## Promoters Evaluated

Promoter	Expected Expression
CAG	Ubiquitous
CBA	Ubiquitous
GFAP	Astrocyte Specific
Synapsin	Neuron Specific

## Components for Optimization

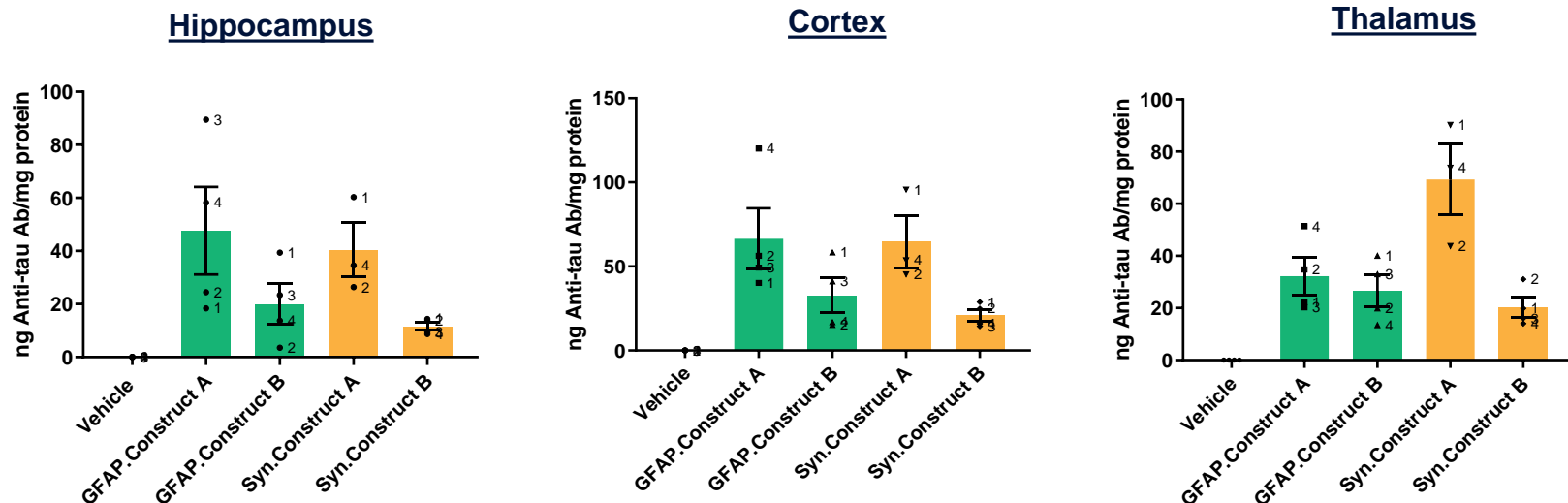
Intron  
Signal peptide sequences  
Ab H- and L-chain order  
Ab H- and L-chain codons  
2A or IRES site  
Cleavage site  
Poly-A  
Stuffer sequence (if needed)

Source: ASGCT 2019 Presentation



# IV Dosing with VOY101 Capsid and Cell Specific Promoters Delivered High Levels of Antibody to Mouse CNS

**Cell-specific anti-tau antibody expression levels significantly higher than levels anticipated with passive immunization<sup>1</sup>**



Evaluation of anti-tau antibody expression on efficacy underway in animal models of Alzheimer's disease

Source: ASGCT 2019 Presentation

IV administration to C57Bl/6J wild-type mice. Results 4-weeks post-dosing.

(1) IV dosing using the VOY101 capsid and cell type-specific promoters resulted in similar levels of anti-tau antibody expression in neurons and astrocytes using ubiquitous or cell-specific promoters. In a previous study conducted by Voyager, anti-tau antibody expression levels in the mouse CNS after IV dosing of a vectorized antibody with a ubiquitous promoter were at least fifteen-fold higher than levels achieved with passive immunization.

# AbbVie Collaboration Targeting Alpha-Synuclein: Overview and Goal

## Overview:

- A hallmark of Parkinson's disease is the accumulation of misfolded alpha-synuclein that can eventually lead to the formation of protein deposits and progressive neurodegeneration
- Approaches to interfere with this process could potentially delay the progression of Parkinson's disease and other synucleinopathies including Lewy Body Dementia and multiple system atrophy
- Only very low levels of anti-alpha-synuclein monoclonal antibody may reach the brain parenchyma from the systemic circulation

## Goal :

- *Deliver a one-time administration of a vectorized monoclonal antibody directed at pathological species of alpha-synuclein for the potential treatment of Parkinson's disease and other diseases (synucleinopathies) characterized by the abnormal accumulation of misfolded alpha-synuclein*

# Value-Driving Events for 2019

Milestone	Timing
Provided update on Type B meeting for VY-AADC	✓
Announced collaboration with Neurocrine Biosciences	✓
Announced collaboration with AbbVie	✓
Provided 12-month data from 8 patients dosed by posterior-trajectory method	✓
Announced restructuring of gene therapy relationship with Sanofi Genzyme	✓
Enroll RESTORE-1 Phase 2 trial for VY-AADC	2019
Provide longer-term data from Phase 1b trial for VY-AADC	2019
Announce selection of two discovery targets with Neurocrine	2019
Advance Huntington's disease programs towards IND filing	2019