Corporate Presentation

September 2019

Forward-Looking Statements

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Senior Executive Team With Deep Experience

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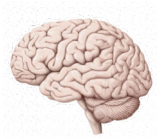
Roche Pfizer

Allison Dorval
Chief Financial Officer

juniper PHARMACEUTICALS Insulet

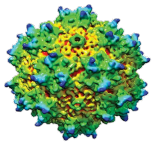
Convergence of Neuroscience and Gene Therapy



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

Voyager



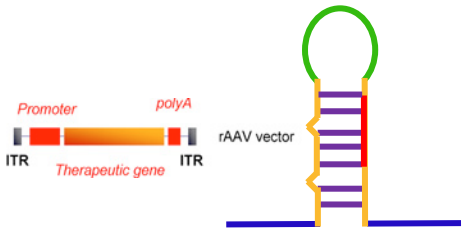
AAV Gene Therapy

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

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

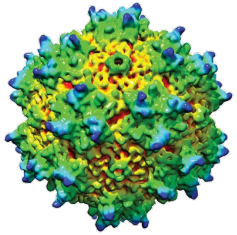
Gene Therapy Development Requires Multiple Optimizations

"Right Tissue, Right Cells, Right Amount, Right Time



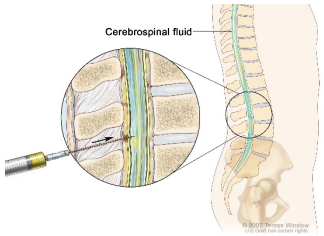
Vector Genome Design

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



AAV Capsid Selection

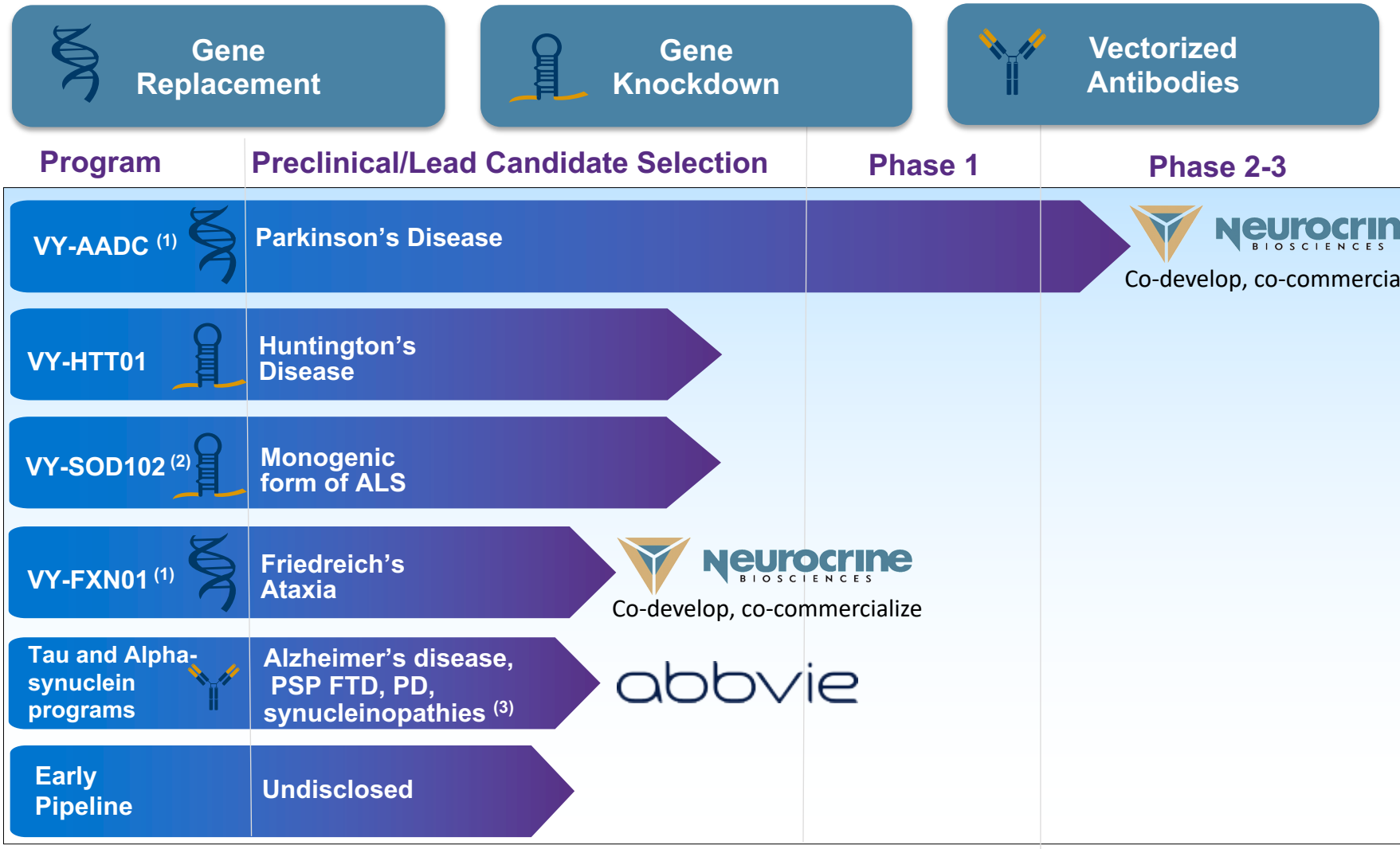
Tropism for relevant tissue and cell types



Delivery Optimization

Translatable dosing paradigm that provides target distribution profile in relevant tissues

AAV Pipeline Focused on Severe Neurological Diseases Across Three Therapeutic Modalities



(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

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

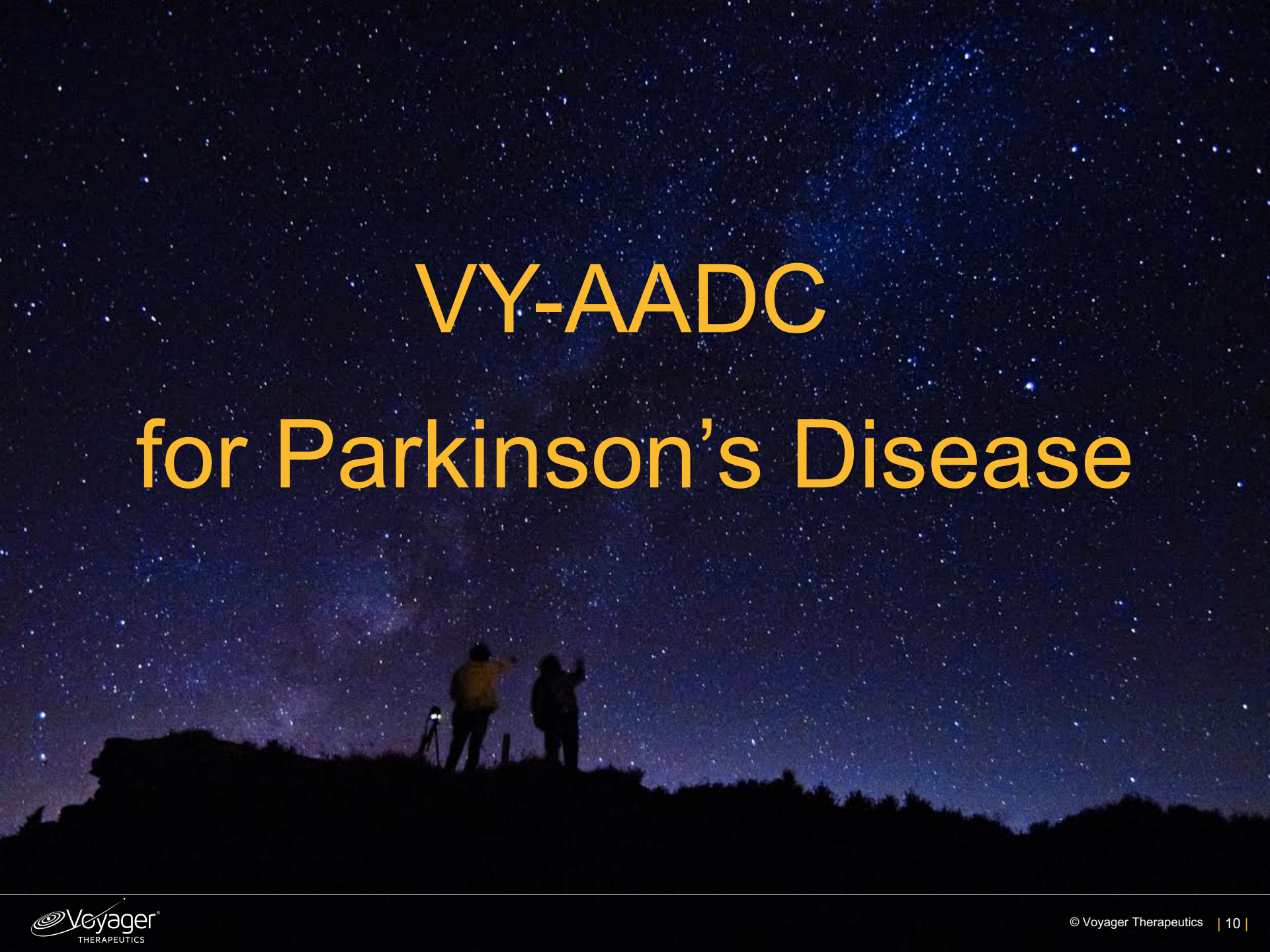
SANOFI GENZYME

Key terms:

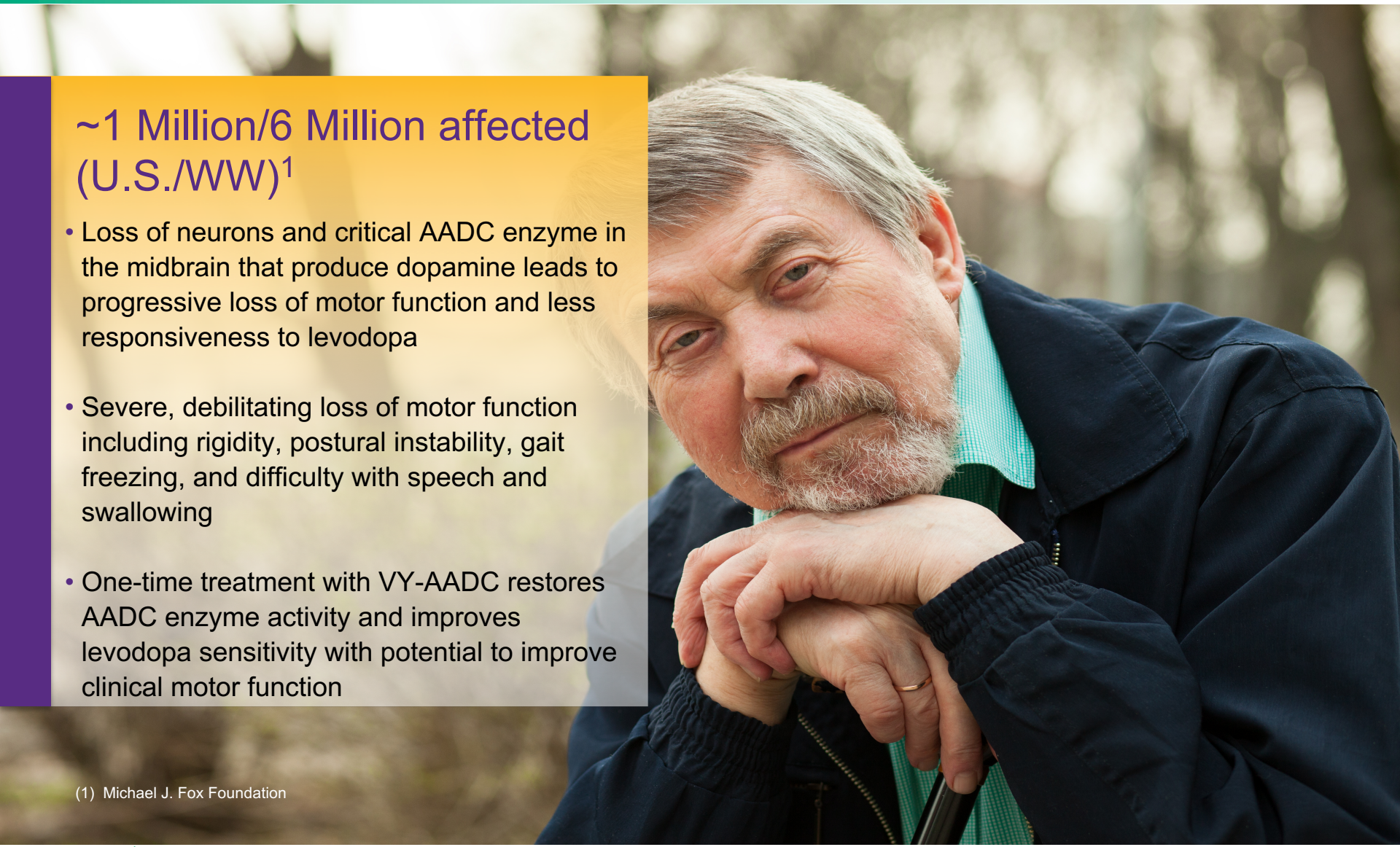
- Gained worldwide rights to the VY-HTT01 Huntington's disease program
- Gained ex-U.S. rights to the VY-FXN01 Friedreich's ataxia program, which are assigned to Neurocrine Biosciences
- Terminated Sanofi Genzyme's option to acquire development and commercialization rights to a future Voyager CNS orphan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

Strong Relationships with Key Advocacy Groups

Relationships with national groups, local chapters, study site networks and other patient groups to enhance awareness and gain insight from the people impacted every day



Parkinson's Disease Overview

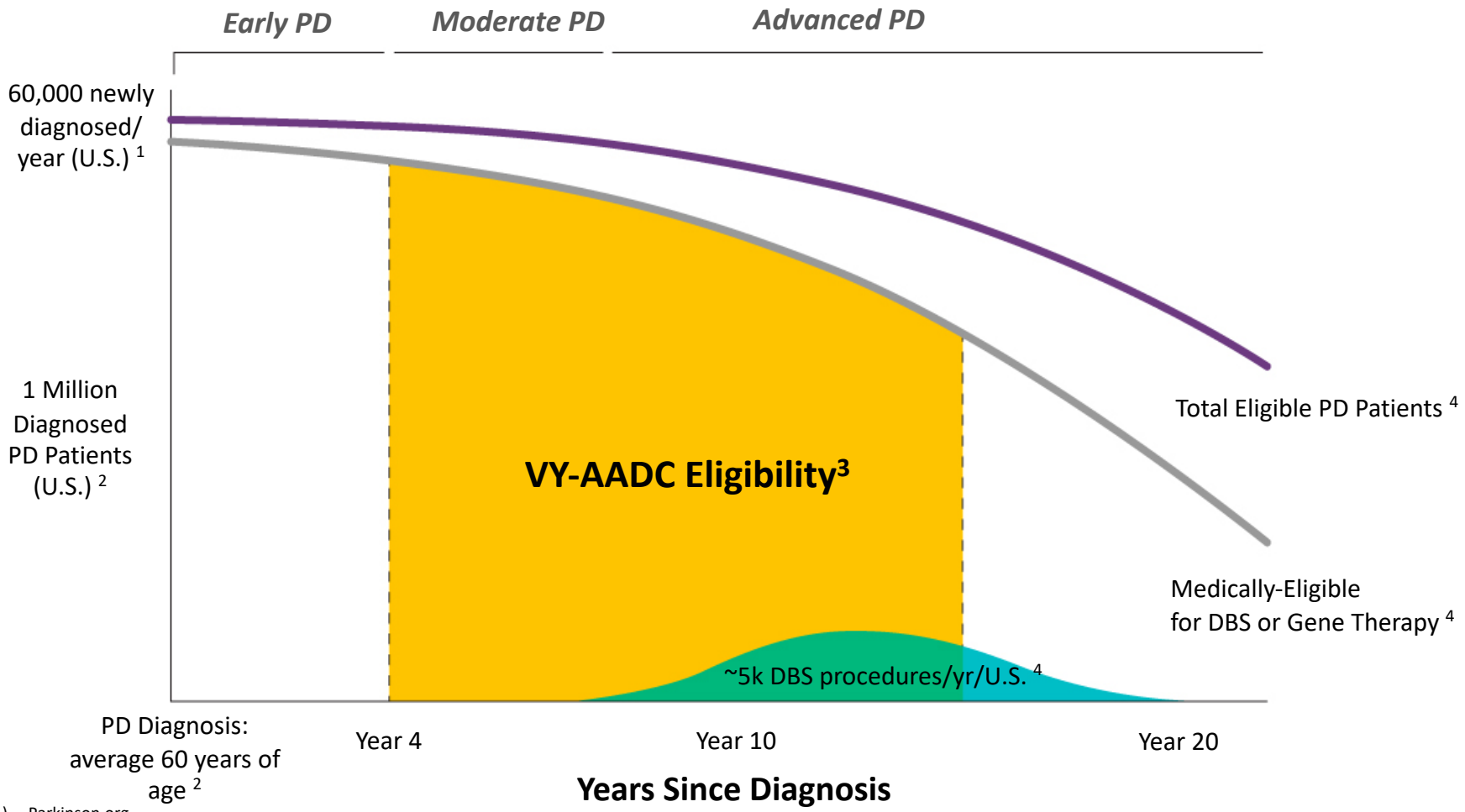


~1 Million/6 Million affected (U.S./WW)[1]

- 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

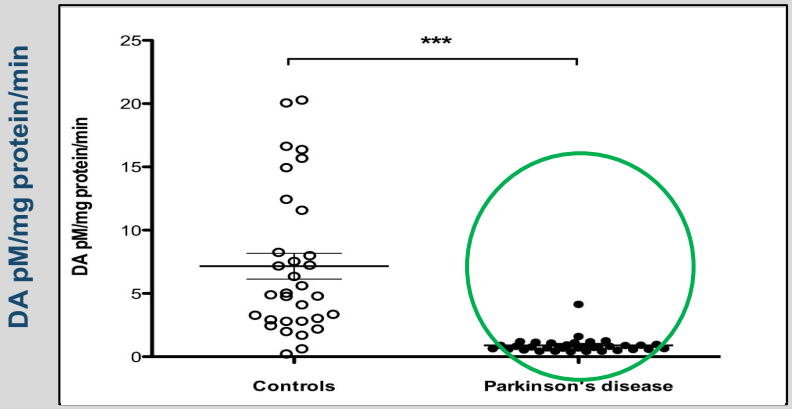
Large Unmet Need in Moderate to Advanced PD

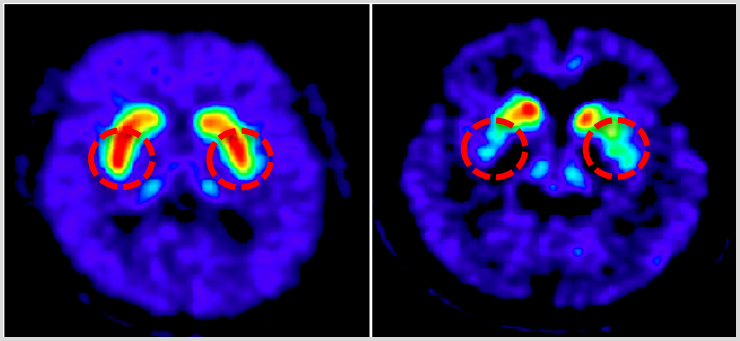


(1) Parkinson.org
(2) Michael J. Fox Foundation
(3) VY-AADC Phase 2 eligibility > 4 years since diagnosis > 3 hours diary OFF time
(4) Voyager estimates

Declining AADC Activity Correlates with Declining Motor Function

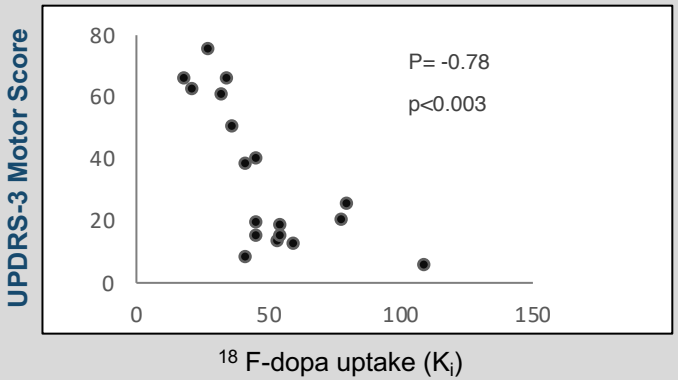
AADC activity in the Putamen[1]



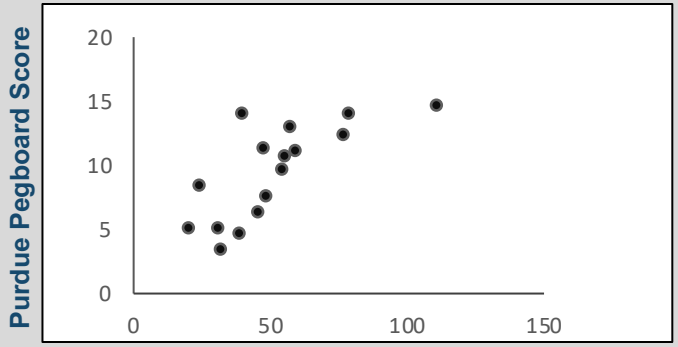


Control[2] PD patient[2]

AADC activity in the Putamen[1]



^{18} F-dopa uptake (K_i)



^{18} F-dopa uptake (K_i)

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

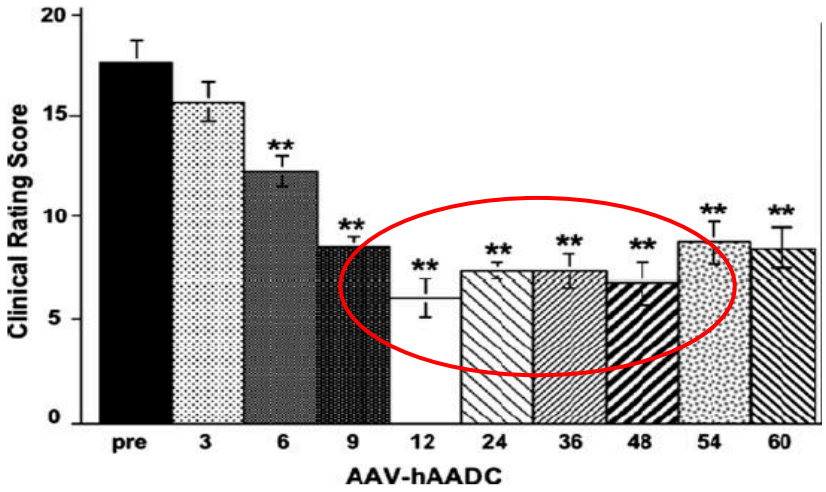
Lower AADC activity correlates with worse motor symptoms and vice versa

(1) K. Bankiewicz, Ribeiro (2002)
(2) Feinstein Institute for Biomedical Research

AAV2-AADC: Dose and Temporal Response in NHPs

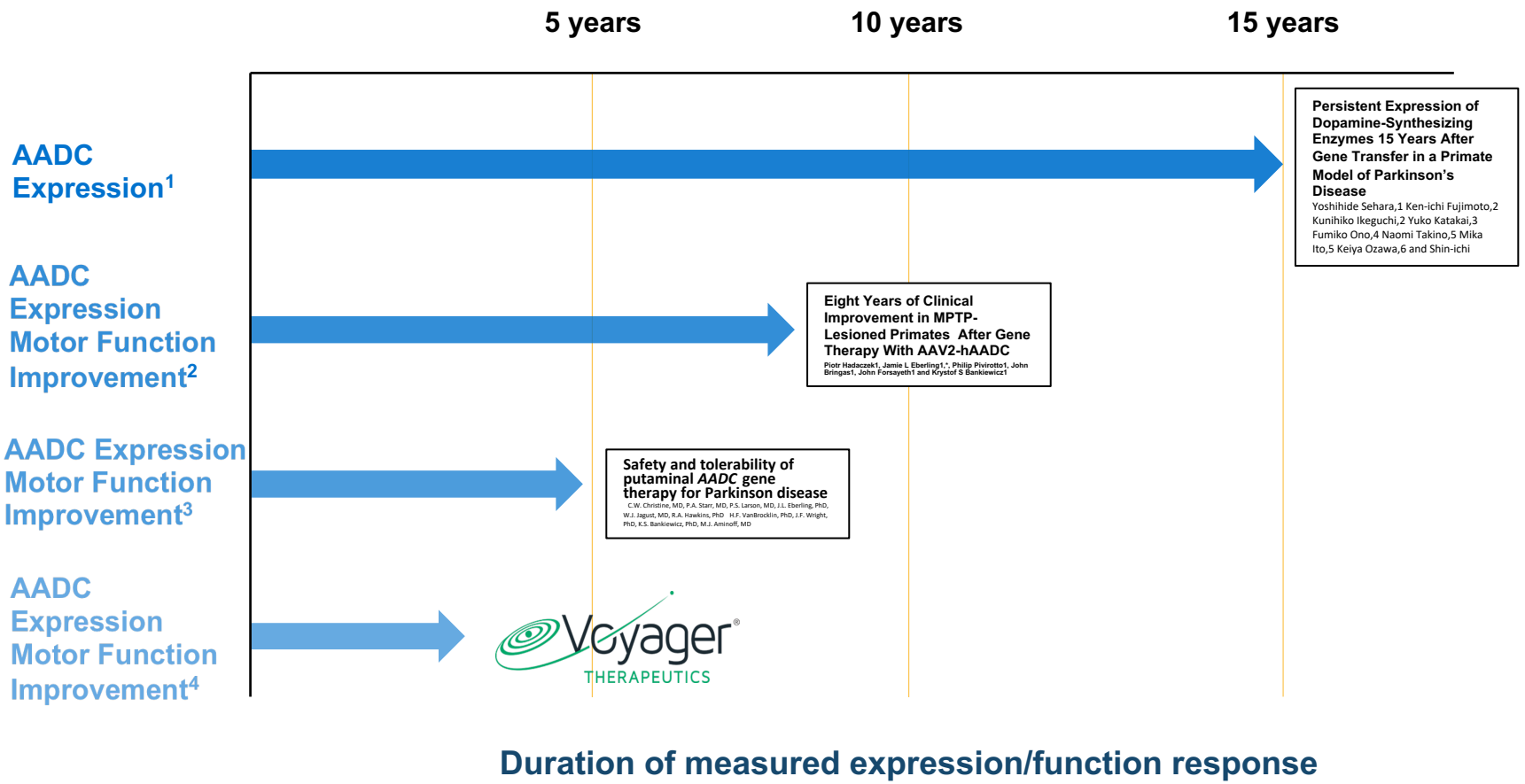
Clinical rating scores improves over 12 months in response to AADC and is durable

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



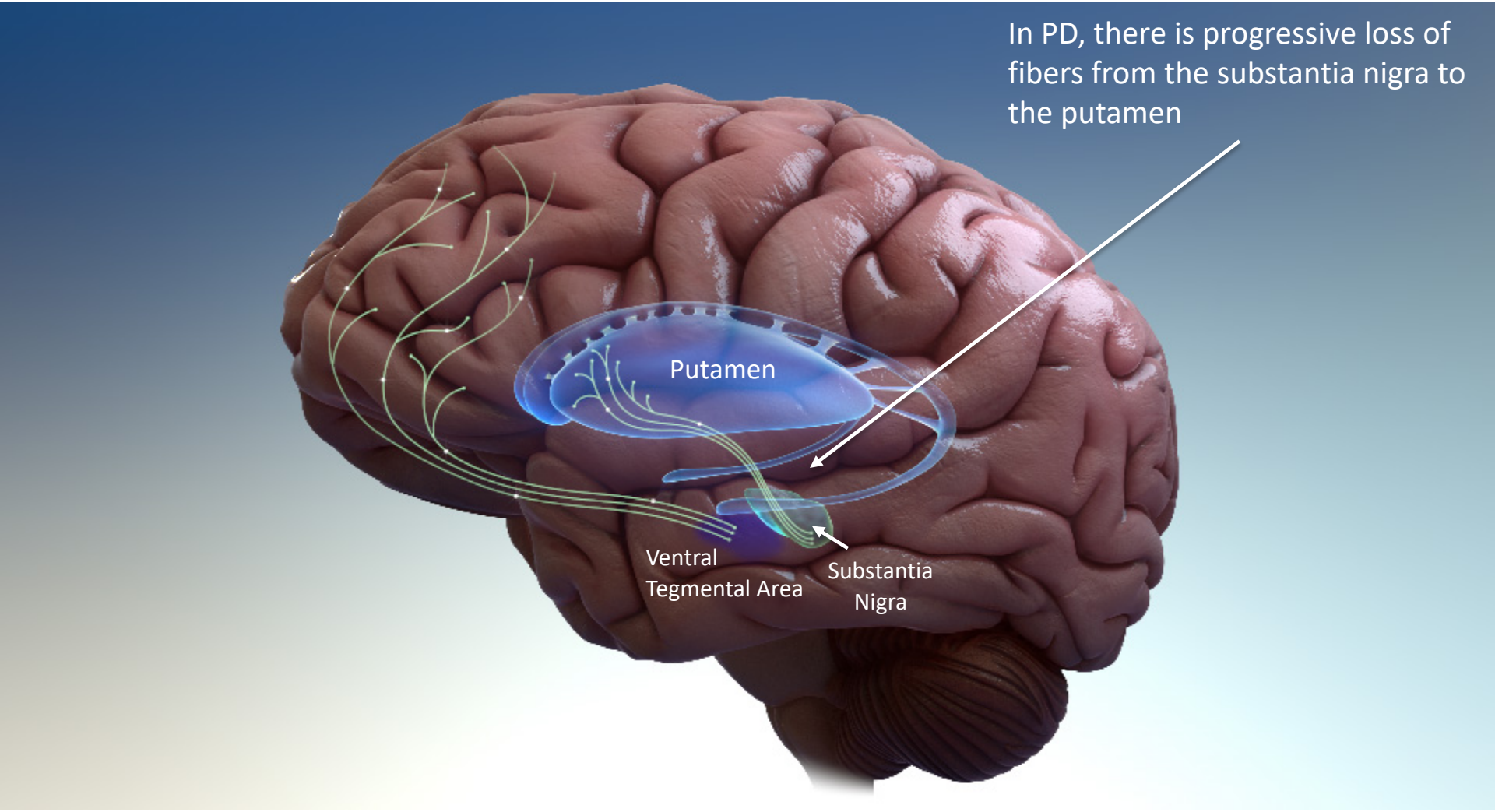
Bankiewicz, 2006

Durable AADC Enzyme Expression/Motor Function Response



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

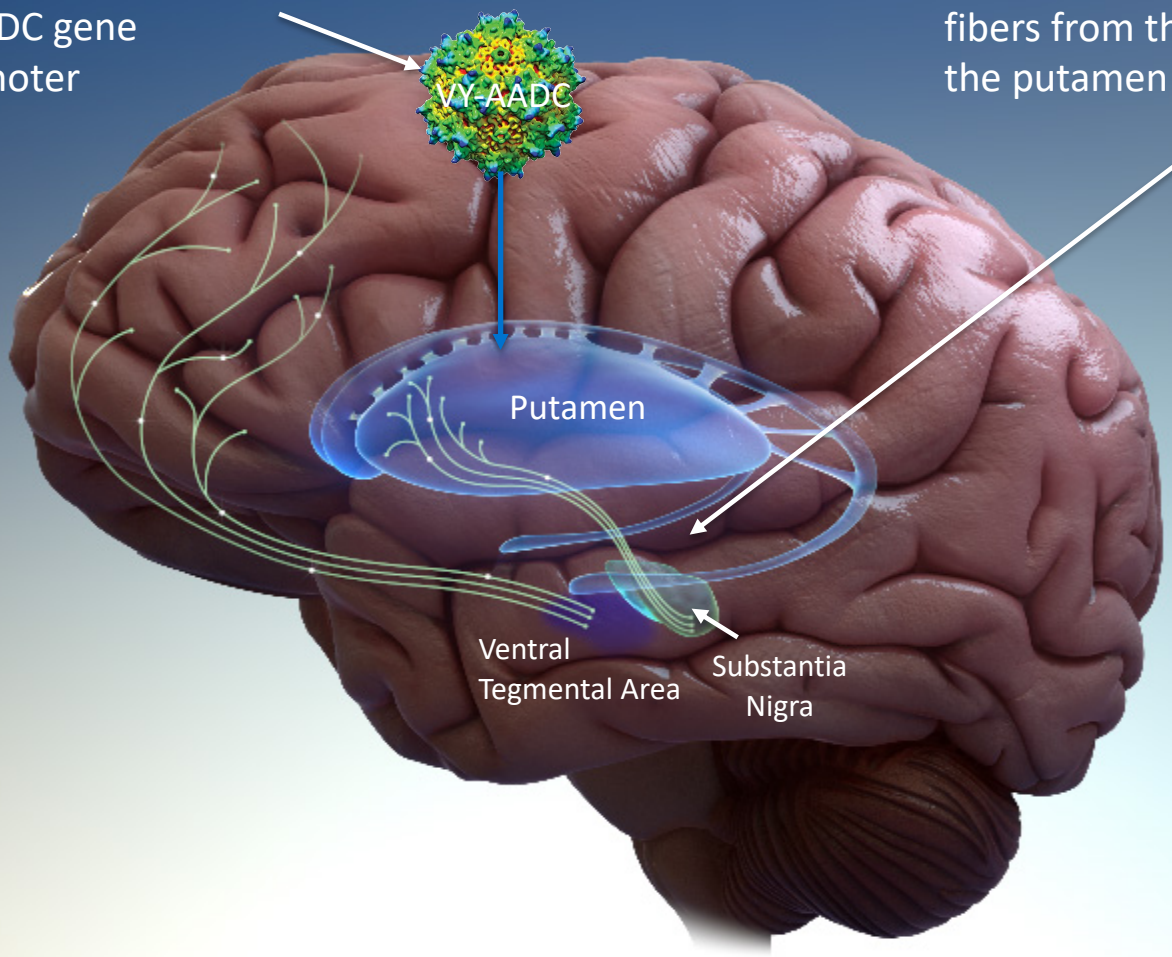
The Ability to Make AADC is Lost as PD Advances



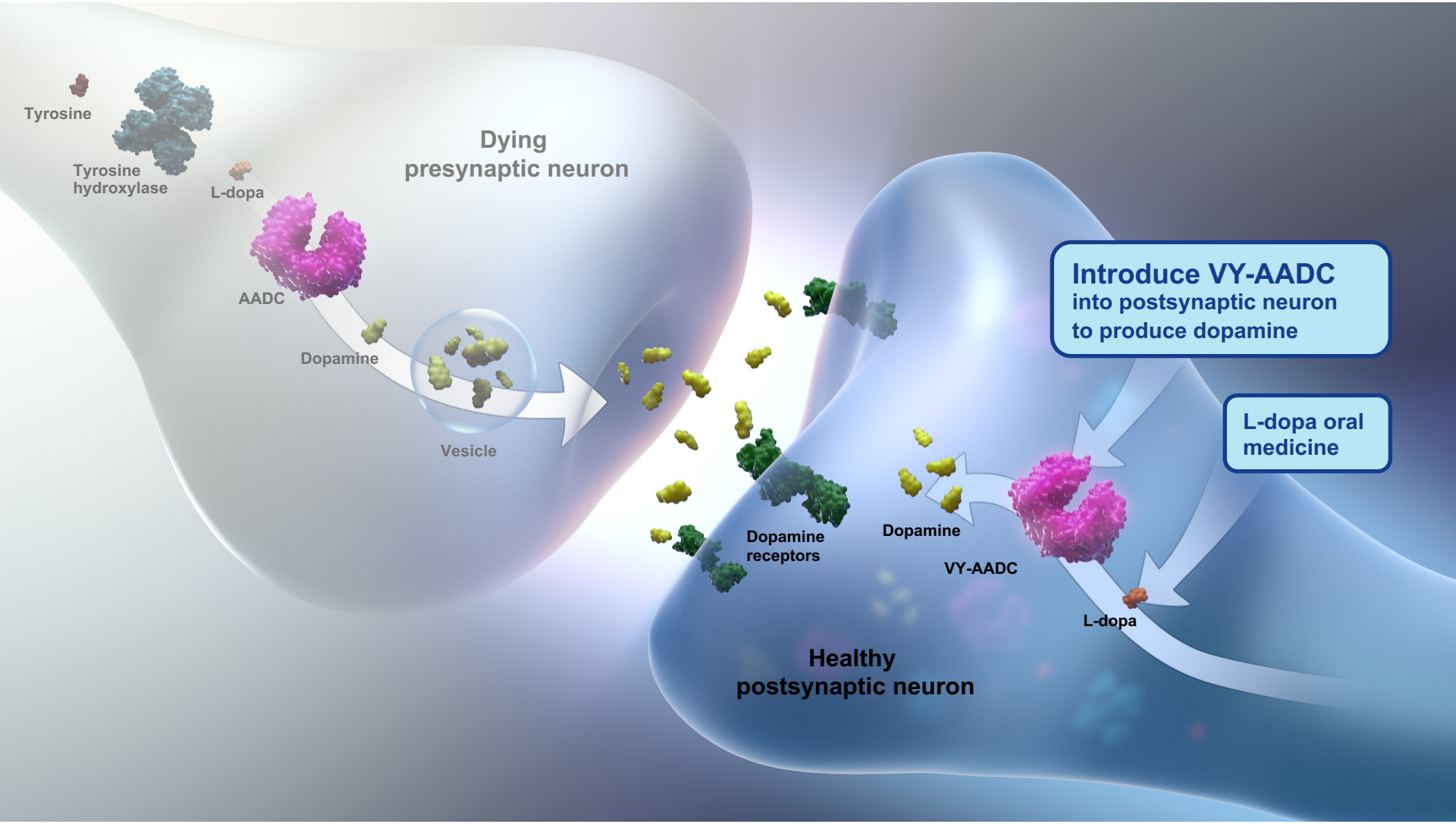
Introduce AADC to Healthy Postsynaptic Neurons in the Putamen

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

In PD, there is progressive loss of fibers from the substantia nigra to the putamen



The Role of the AADC Enzyme

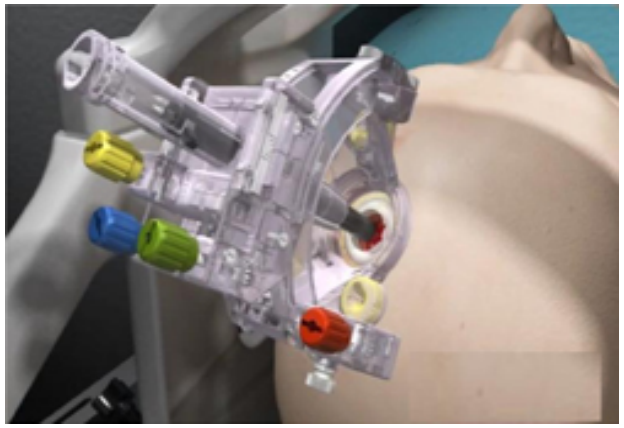


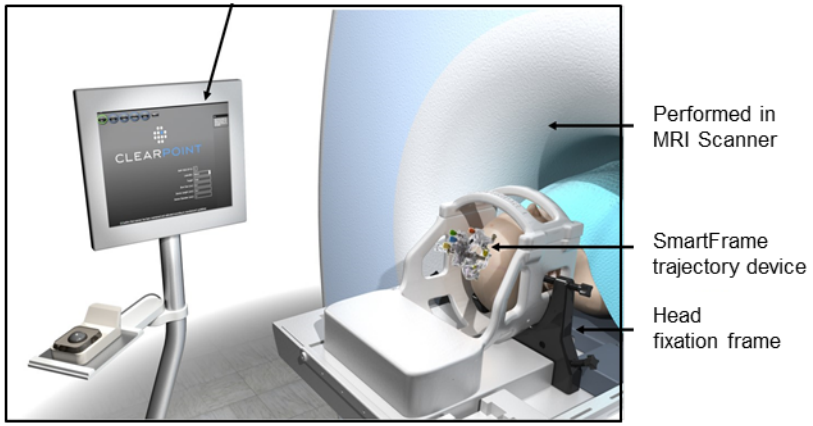
Key Phase 1b (PD-1101) Objectives with VY-AADC

1. Exposure:
   - Safely achieve ≥30% coverage of the putamen with MRI-guided infusions

2. Target engagement and pharmacology:
   - Obtain increased enzyme activity with ^{18}Fdopa and PET
   - Achieve enhanced response to levodopa through decreased dose requirements and response to IV levodopa

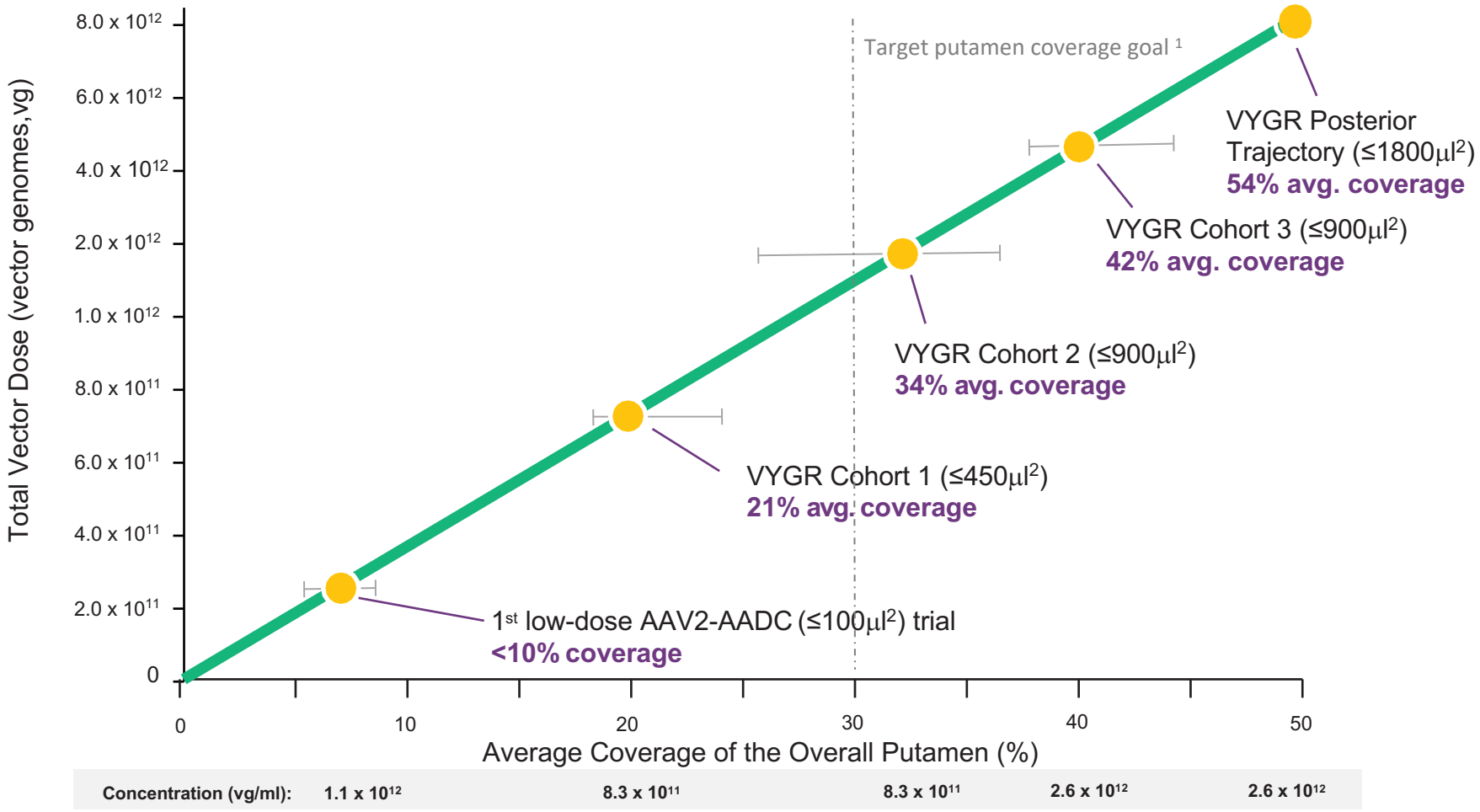
3. Clinical profile:
   - Achieve dose and temporal responses across key clinical endpoints





Source: MRI Interventions

Thorough Phase 1b Dose Escalation

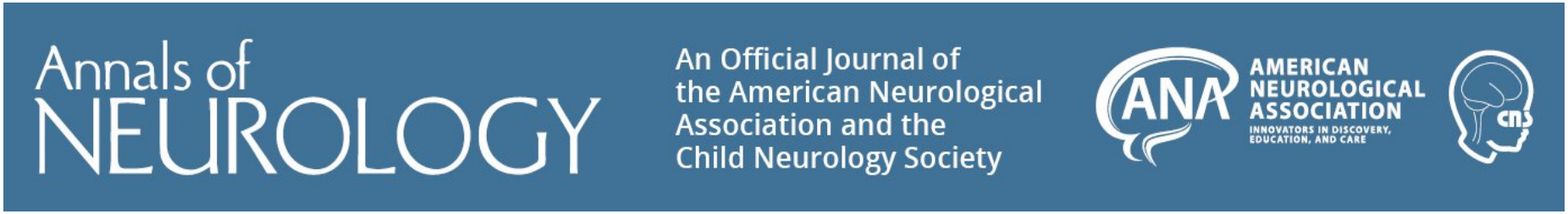


Source: Christine, CW. Neurology 2009; 73:1662-1669, Voyager Therapeutics June 22, 2016 and January 20, 2017 press releases

(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*



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

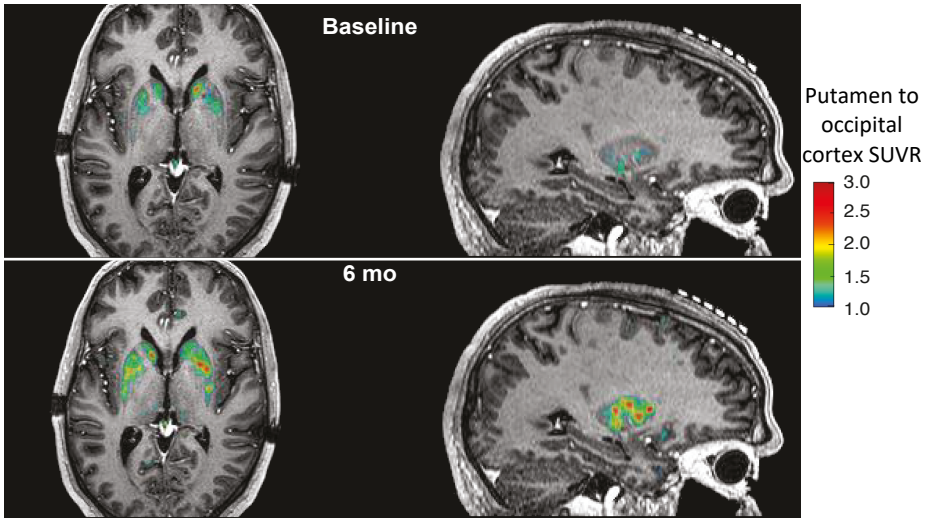
Patients representative of advanced stages of Parkinson's disease population

	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[(1)] mg	1467.5 (615.0)	1635.5 (687.3)	1476.5 (429.1)	1500.9 (179.2)

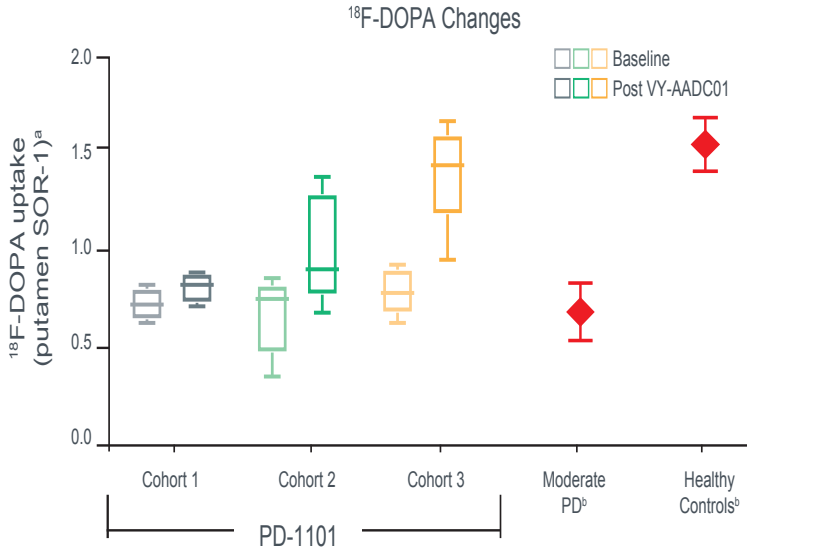
Source: Voyager Therapeutics and Christine, C. W., et al., (2019), Ann Neurol. doi:10.1002/ana.25450, and AAN 2019 Van Laar Poster
(1) Levodopa Equivalent Dose
Mean (standard deviation)

Change in AADC Activity in the Putamen

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



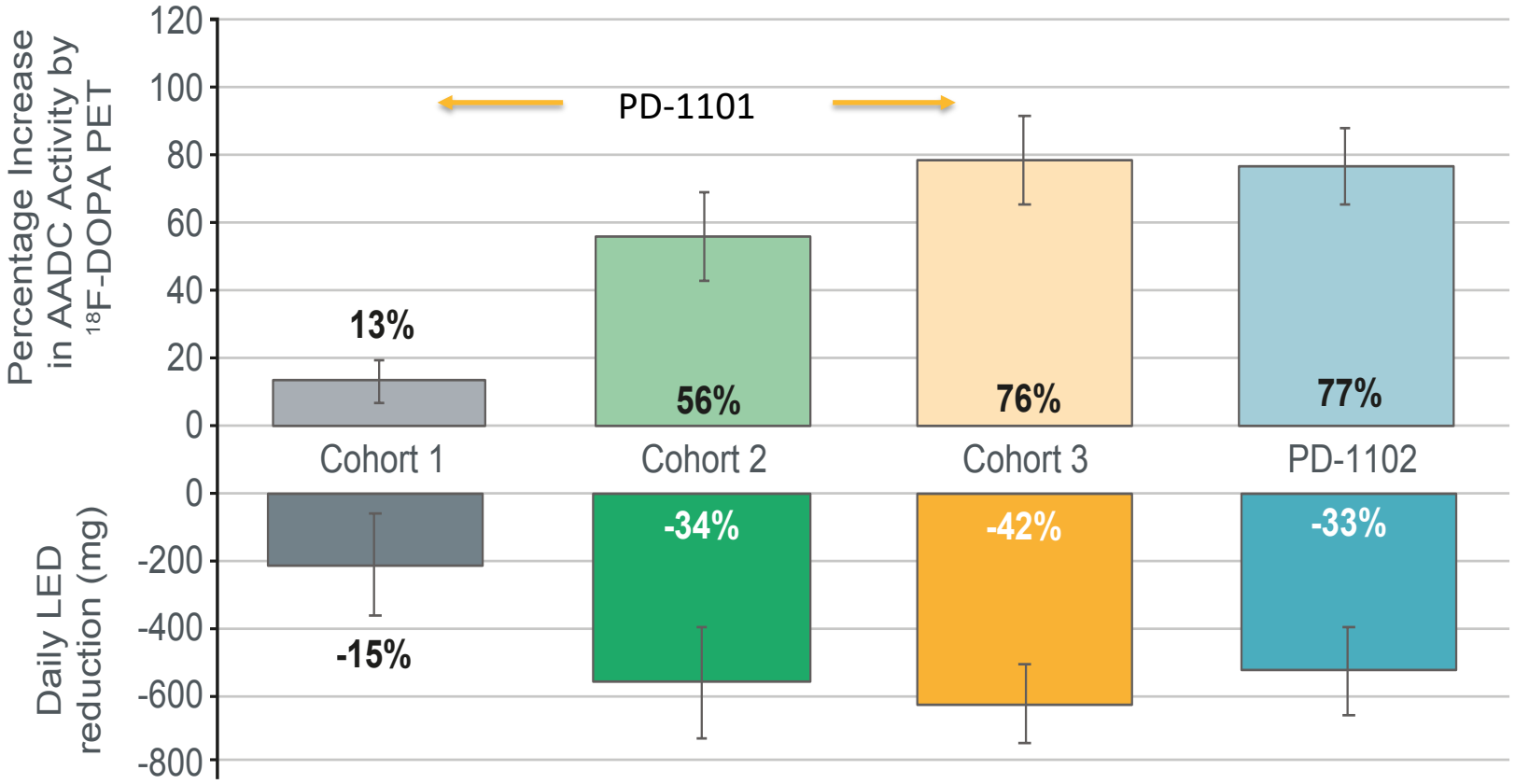
PET, Positron Emission Tomography



Imaging frames captured 65–75 min after ^{18}F-DOPA administration. [a]Standardized uptake ratios (SORs) were calculated using bilaterally averaged occipital time-activity curve (kBq/mL) region-of-interest values in each subject; [b]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

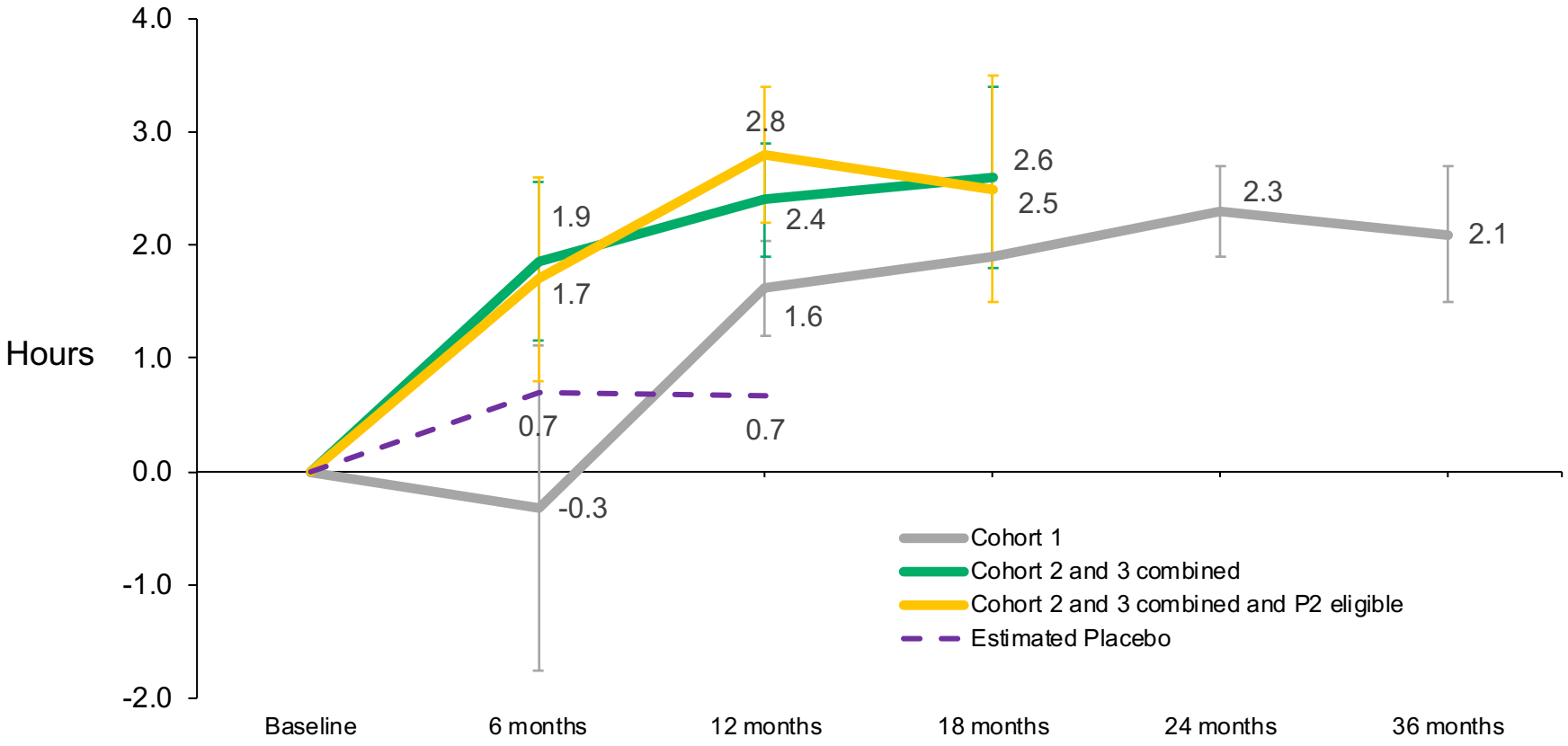
Good ON time: hour improvement from baseline (SE)	*Baseline*	*12-months*	*18-months*	*2-years*	*3-years*
Cohort 1, n=5	10.5 (1.0)	1.6 (0.4)	n/a [1]	2.3 (0.4)	2.1 (0.6)
Cohort 2, n=5	10.6 (0.8)	3.3 (0.6)	3.5 (1.1)	2.7 (1.4)	
Cohort 3, n=5	10.3 (0.7)	1.5 (0.5)	1.7 (1.1)		
PD-1102 Post Traj n=8	9.1 (0.5)	1.7 (0.5)			
Cohorts 2-3, n=10	**10.5** (0.5)	**2.4** (0.5)	**2.6 (0.8)**		
Cohorts 2-3 w/o severe dyskinesia, n=7	**10.1** (0.5)	**2.8** (0.6)	**2.5 (1.0)**		
PD-1102 Post Traj, w/o severe dys or ICD n=4	**8.8** (0.8)	**3.2** (0.5)			

OFF time and ON time w/ troublesome dyskinesia hour per day (SE)	*Baseline*	*12-months*	*Mean % change*	*18-months*	*Mean % change*
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

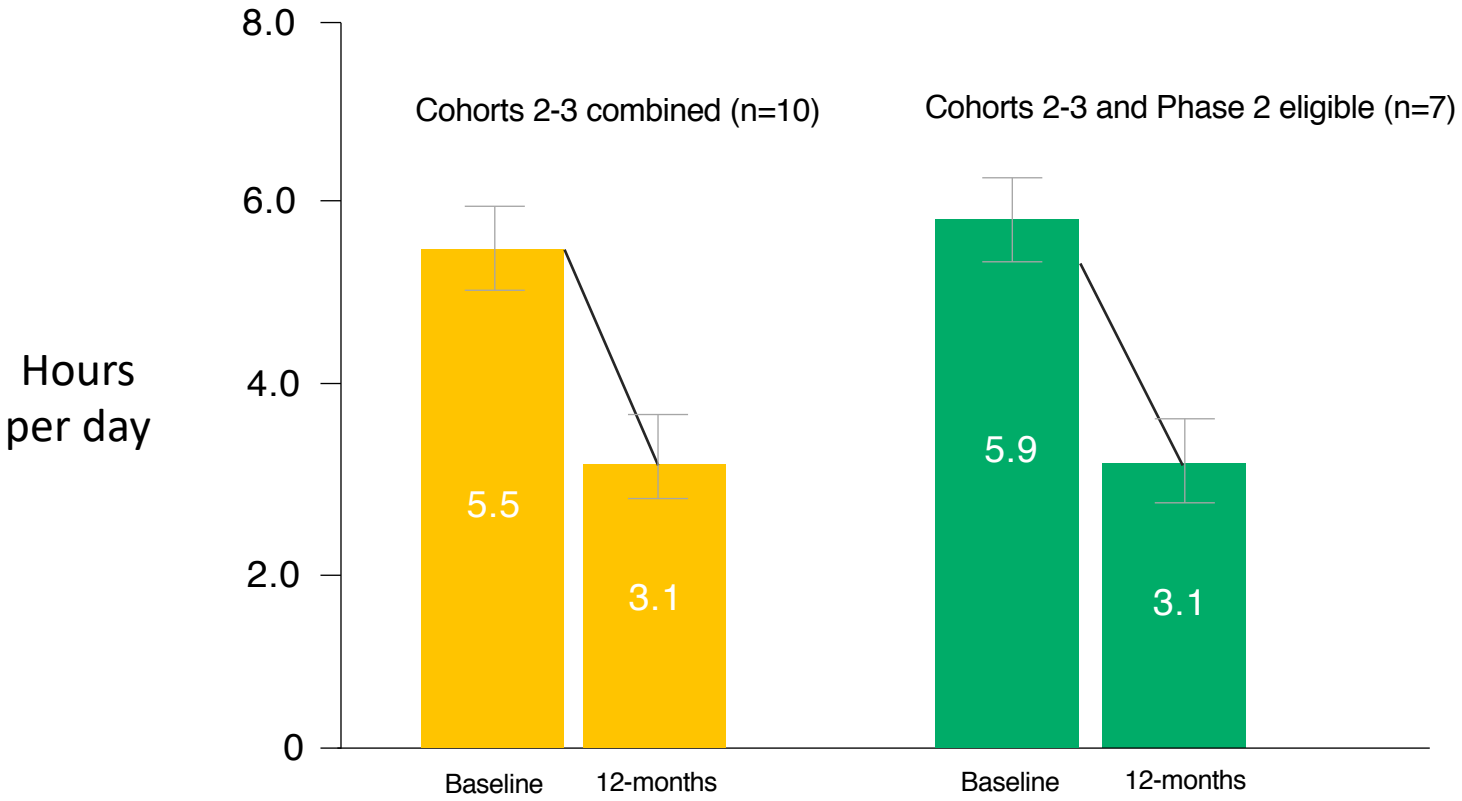
PD-1101: 2.8 hour improvement at 1 year in Cohort 2/3 combined and Phase 2 eligible group (n=7)



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

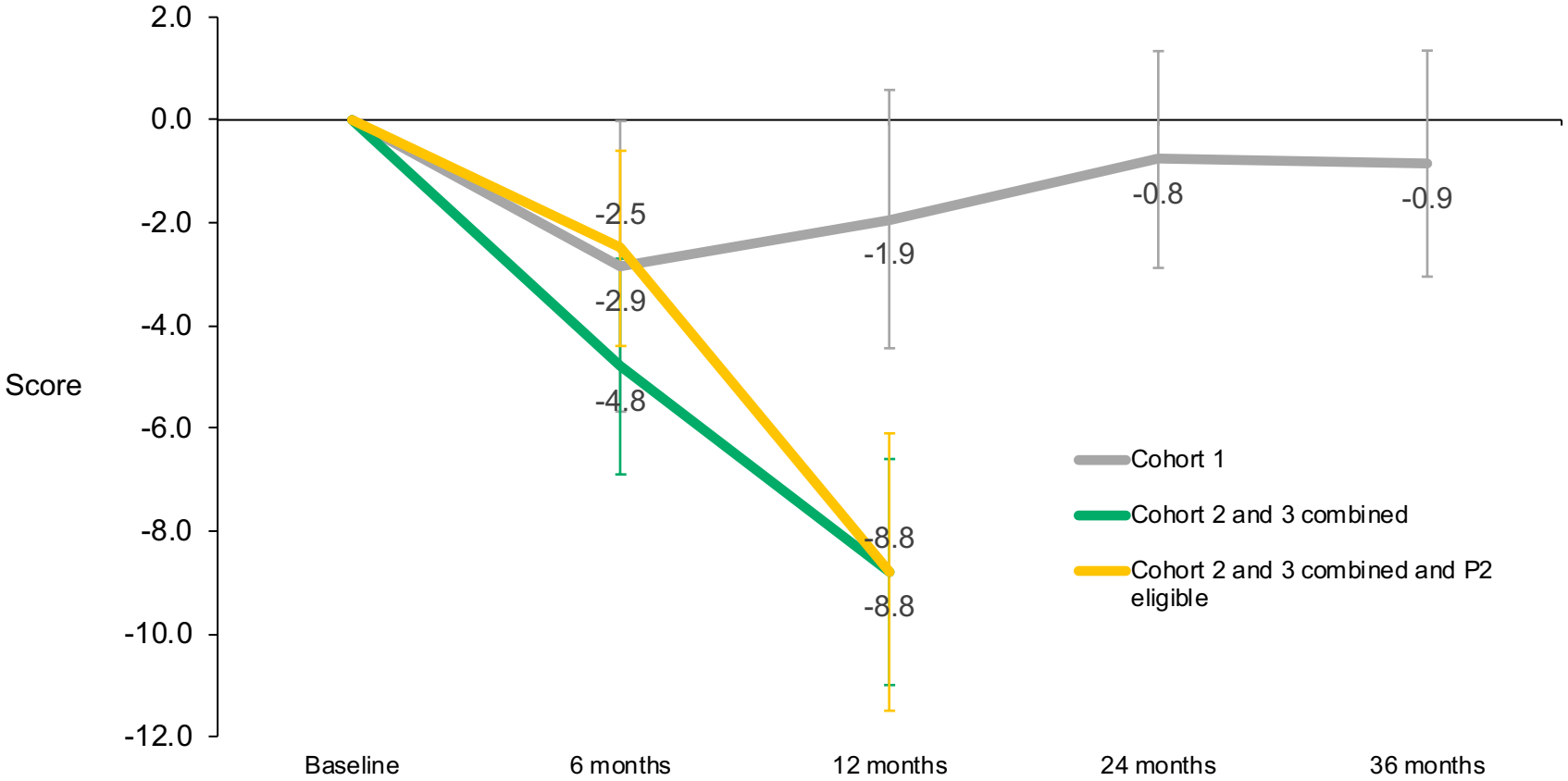
PD-1101: 46% reduction in OFF time and ON time w/ troublesome dyskinesia at 1 year



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

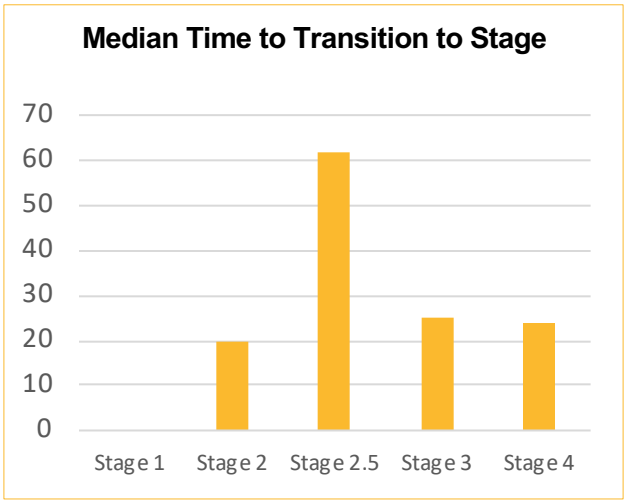


Source: Voyager Therapeutics
Note: Full Cohort 2 and 3 data at 24 months not yet available

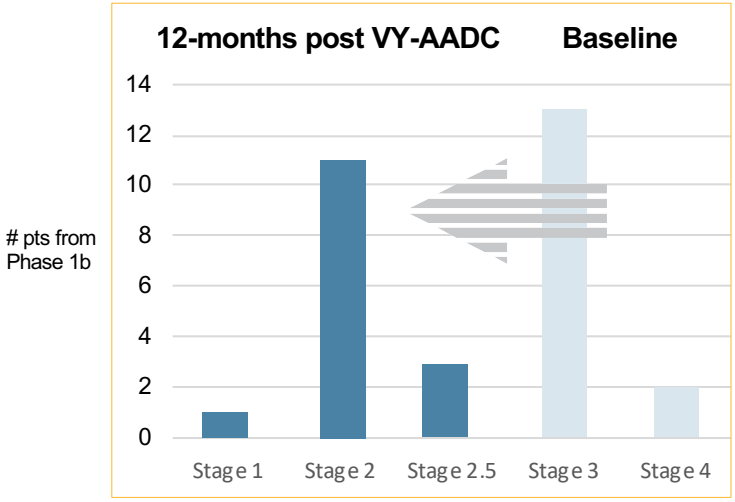
VY-AADC Phase 1b: Shift in Disease Staging

Observed shift in disease progression based on mH&Y stages[1]

Zhao et al.



VY-AADC Phase 1b results



(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 [1]

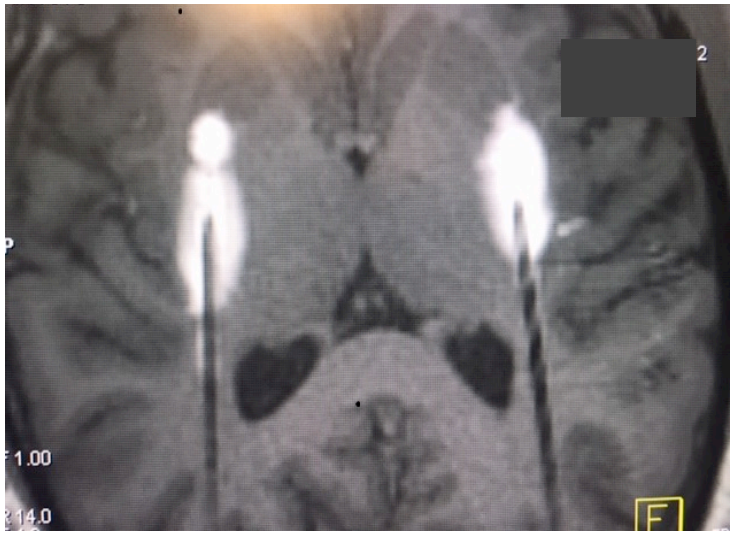
(1) LEDs increased to above baseline in Cohort 1 at 3 years due to a single patient

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)

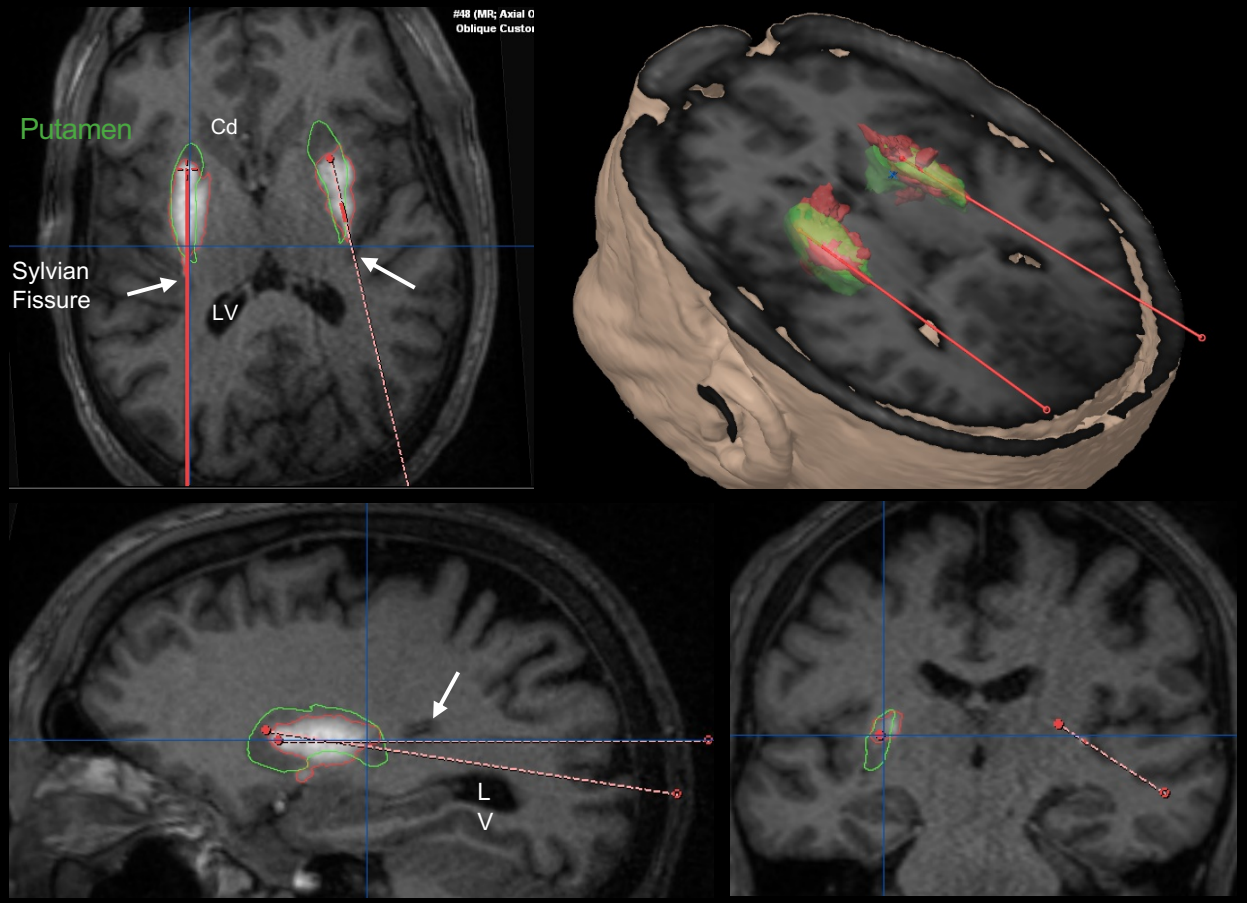
- Completed dosing in 8 patients
- 54% average putaminal coverage
- Reduced infusion time by two hours (from five hours to three hours) compared with PD-1101
- Confirmed the findings from PD-1101 that VY-AADC leads to increases in AADC enzyme activity and improvements in motor function and quality of 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

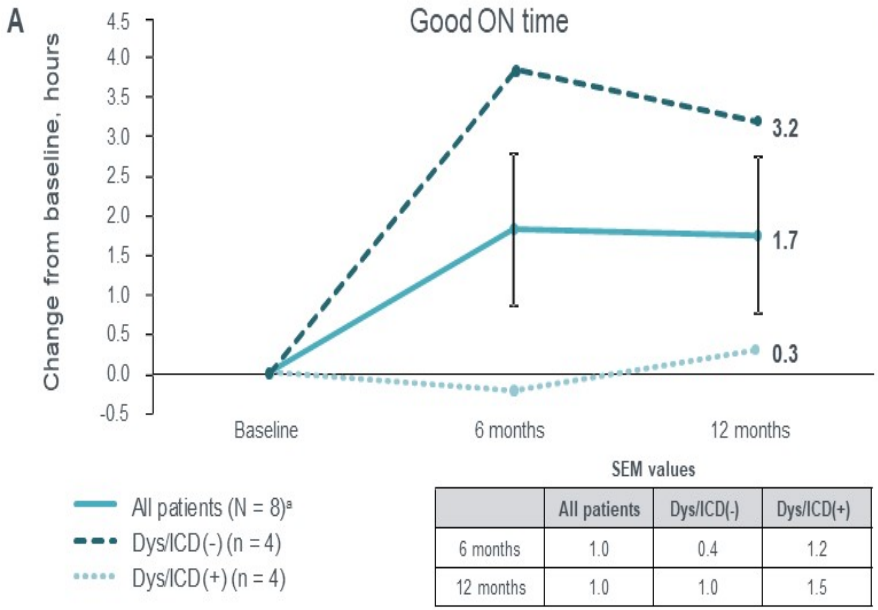
Posterior Trajectory Overview

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



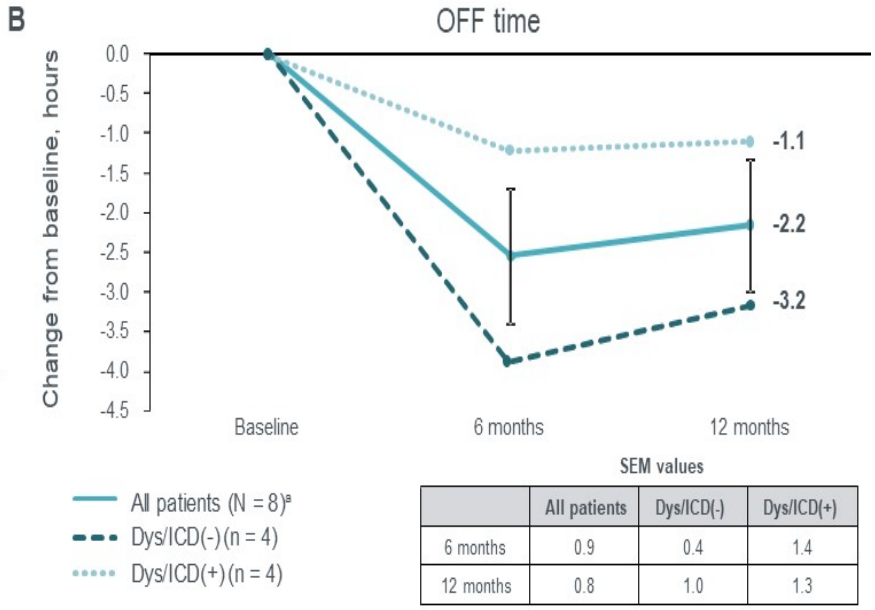
PD-1102 Good ON time and OFF time Results

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



SEM values

	All patients	Dys/ICD(-)	Dys/ICD(+)
6 months	1.0	0.4	1.2
12 months	1.0	1.0	1.5



SEM values

	All patients	Dys/ICD(-)	Dys/ICD(+)
6 months	0.9	0.4	1.4
12 months	0.8	1.0	1.3

[a]Excluding patient who received lower vg concentration, change in good ON time 1.4 ± 1.1 hours and OFF time -1.9 ± 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

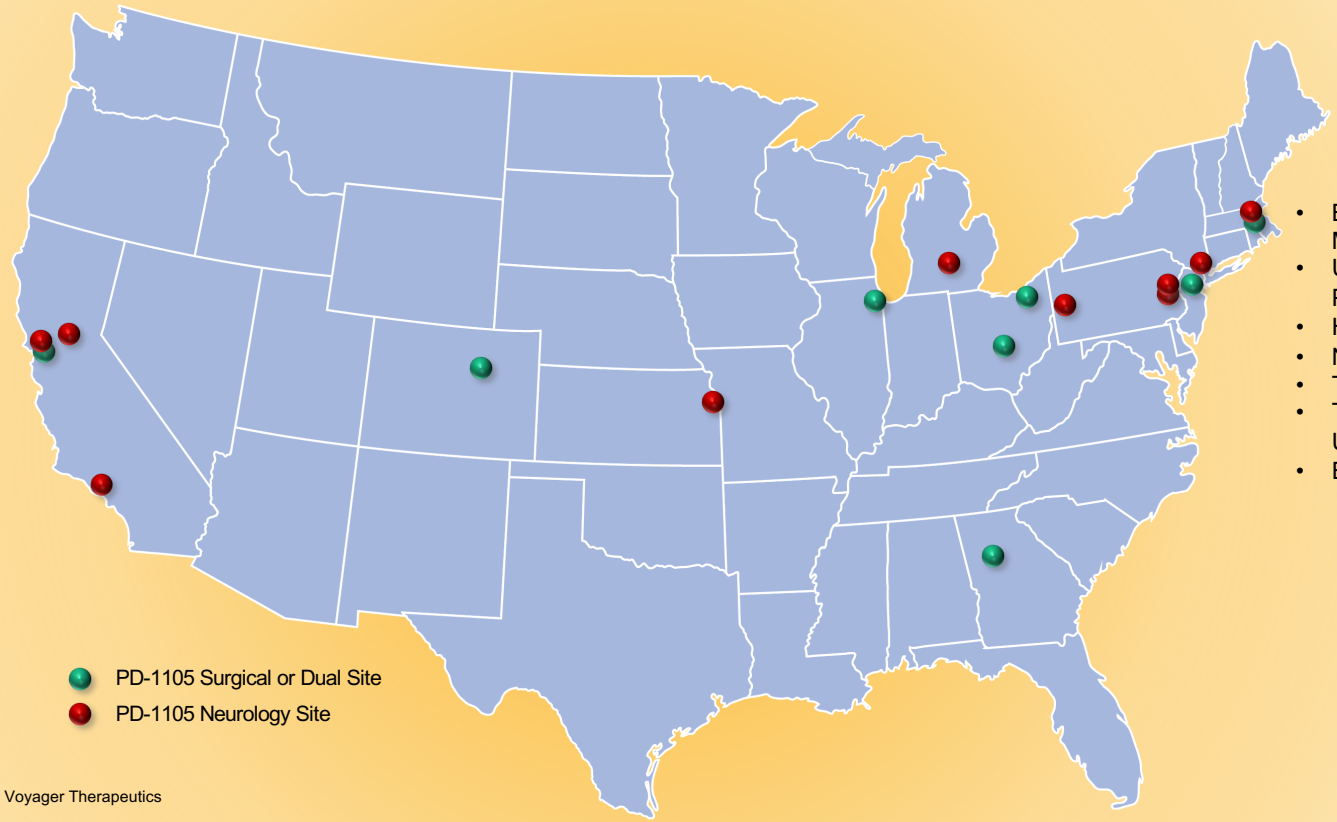
	RESTORE-1 Phase 2/3 Trial of VY-AADC
Trial Size	75 – 100 patients, randomized 1:1 to placebo
Dose	Up to total of 2.5×10^{12} vector genomes
Inclusion Criteria	PD Diagnosis > 4 years $\geq$ 3 hours of OFF time Not responding adequately to oral meds
Primary Endpoint	Good ON time, or ON time without troublesome dyskinesia as measured by self-reported diary
Secondary Endpoints	Diary OFF time Changes in daily doses of oral levodopa Other motor function and QOL measures including UPDRS-II and UPDRS-III scores, PDQ-39, CGI score, NMSS measures
Biomarker Data	VY-AADC putaminal coverage AADC enzyme expression and activity by PET

RESTORE-1 Trial Site Activation On-Track at Top Academic Centers

Over 20 Surgical and Neuro Sites Active with Additional Sites in Progress

- University of Pittsburgh Medical College
- Ohio State
- Cleveland Clinic
- Michigan State
- Northwestern University

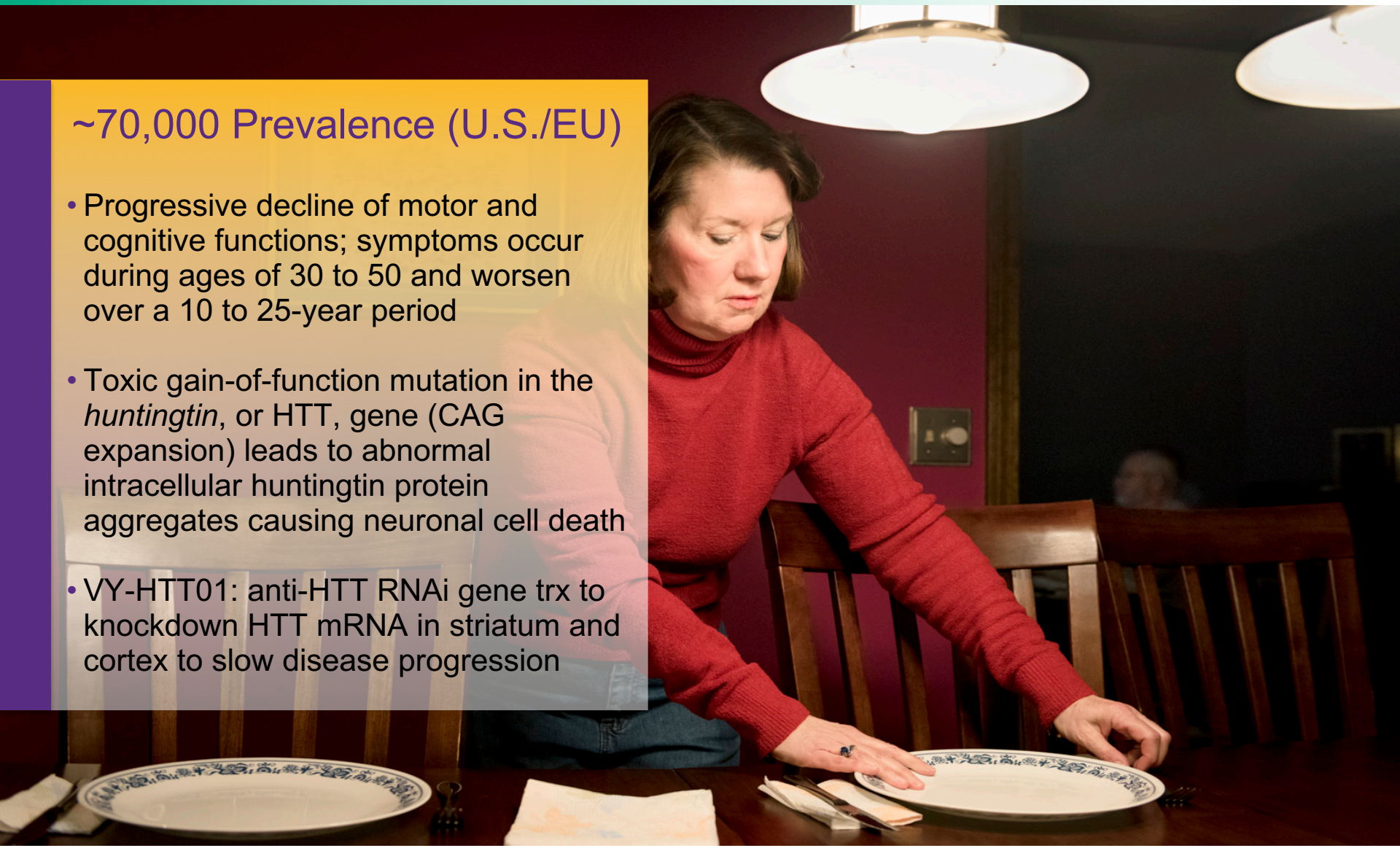
- University of California, San Francisco
- University of Colorado
- University of California, Davis
- University of California, Irvine
- University of Kansas



- Beth Israel Deaconess Medical Center
- University of Pennsylvania
- Hackensack
- New York University
- Tufts University
- Thomas Jefferson University
- Emory University

Source: Voyager Therapeutics

Huntington's Disease Program Overview



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

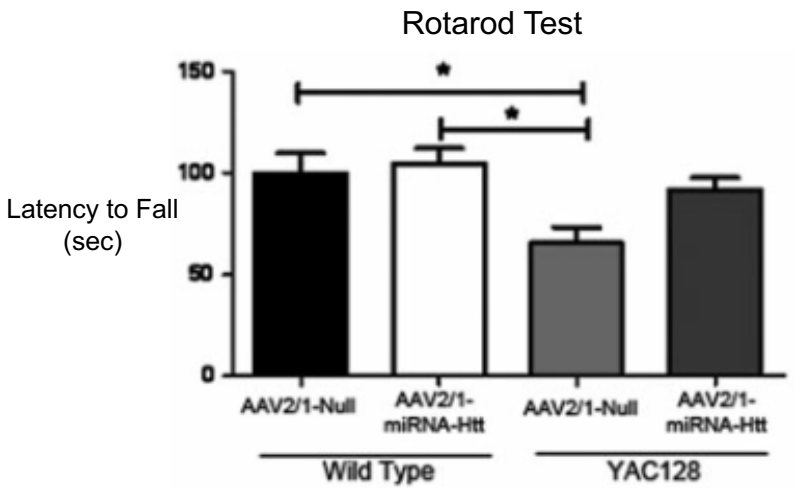
- Progressive decline of motor and cognitive functions; symptoms occur during ages of 30 to 50 and worsen over a 10 to 25-year period
- Toxic gain-of-function mutation in the *huntingtin*, or HTT, gene (CAG expansion) leads to abnormal intracellular huntingtin protein aggregates causing neuronal cell 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

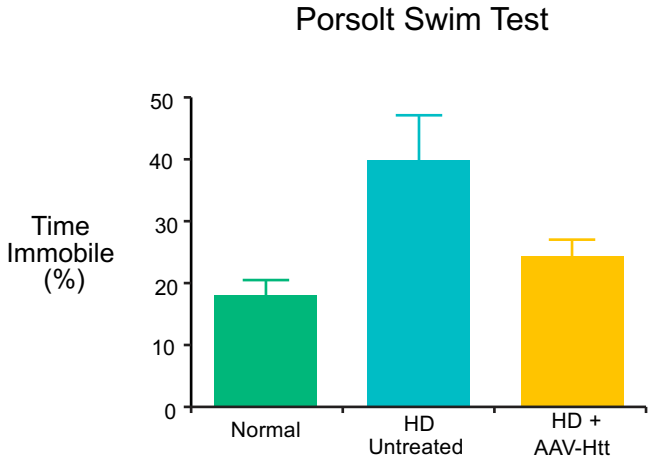
- Mutant huntingtin is causal for disease and has numerous deleterious molecular and cellular effects
- Transgenic models confirm pathogenicity of poly-Q HTT
- RNAi or ASO studies in HD animal models demonstrate that partial lowering of HTT provides potential therapeutic benefit and is well-tolerated

> 40% knockdown of HTT results in significant functional benefit

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



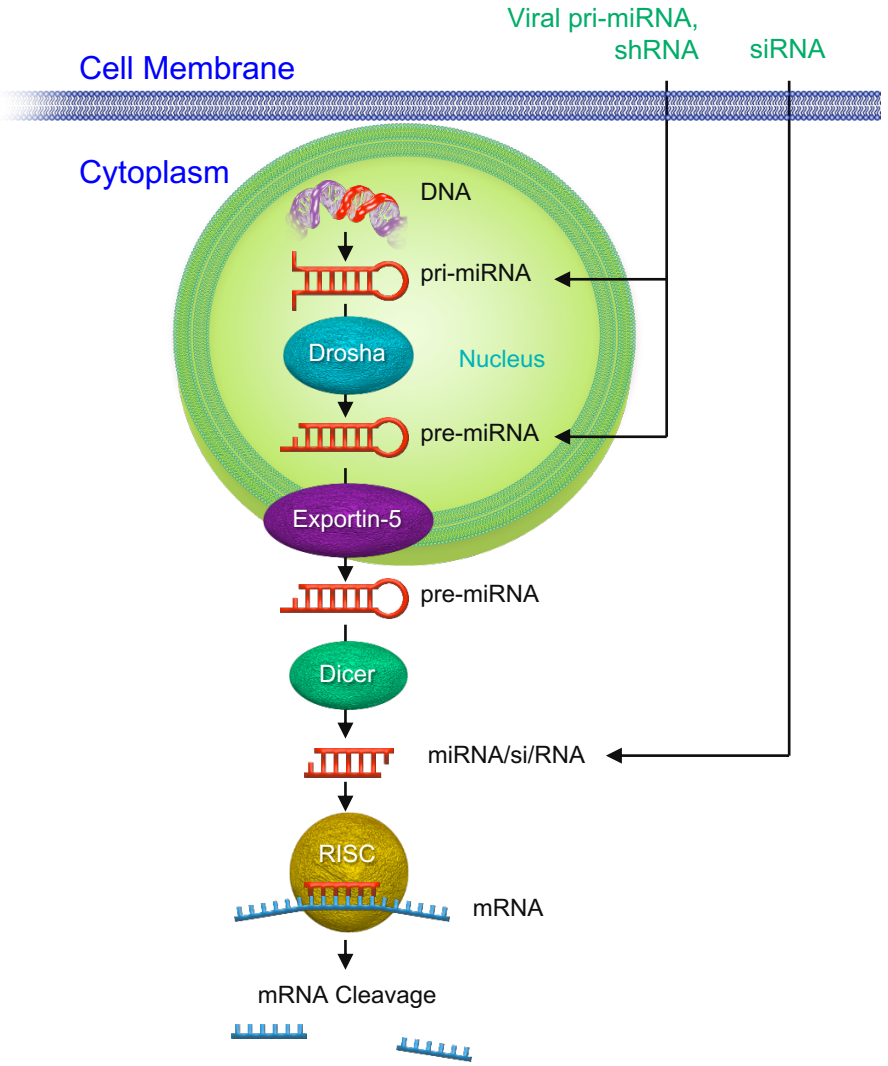
~55% Knockdown of HTT with AAV Normalizes Depressive Behavior in Mouse Model (YAC128)



Source: Stanek et al., 2014

RNAi Mechanism of an HTT-Lowering AAV Gene Trx

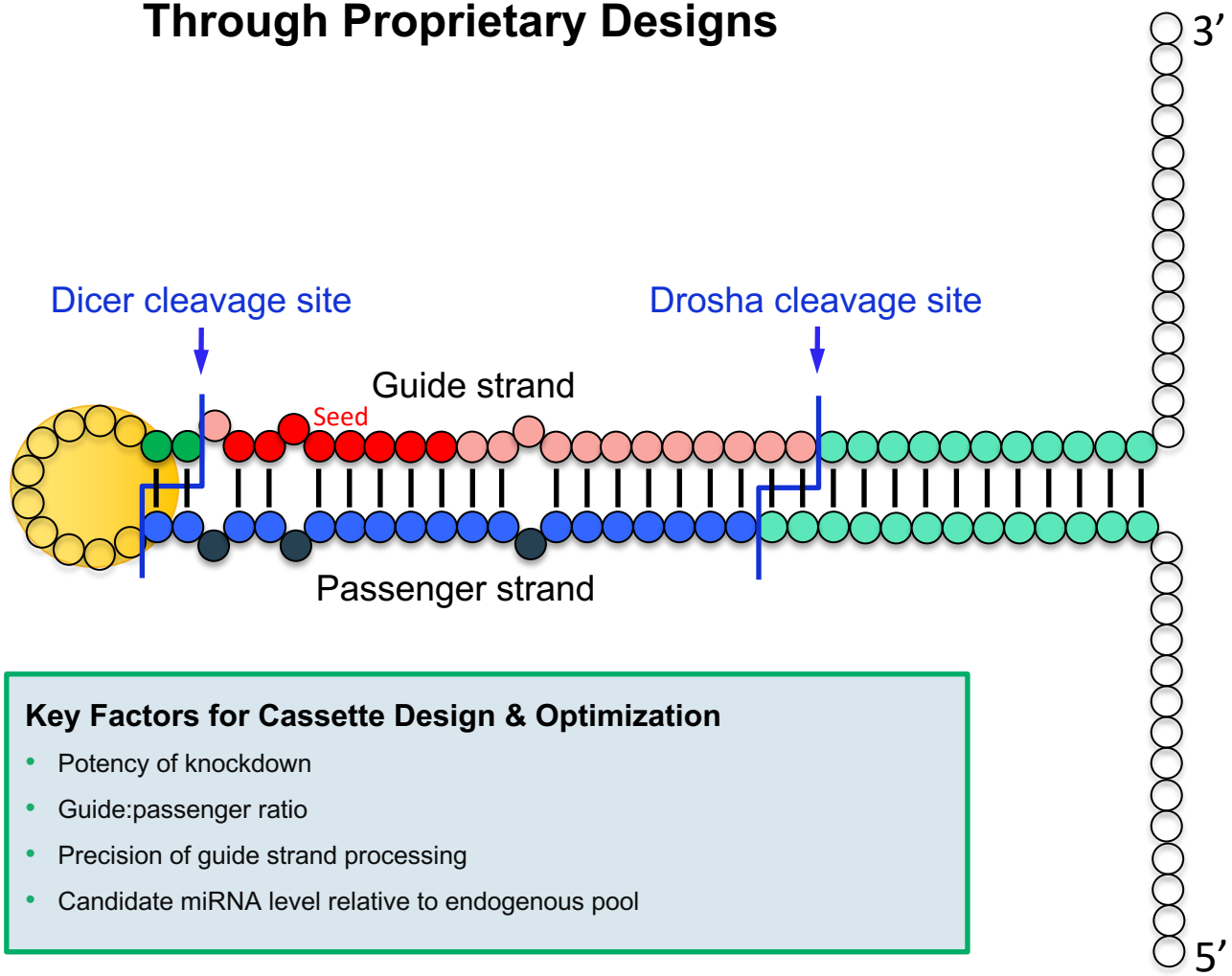
- Pri-miRNA (with flanking regions) or pre-mRNA/shRNA (no flanking regions) are virally delivered (e.g. by AAV)
- Expressed pri-miRNA or pre-miRNA are processed by the cell's endogenous pathway to a miRNA duplex
- miRNA duplex unwinds, binds to its complementary HTT mRNA substrate, and recruits the RNA-Induced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



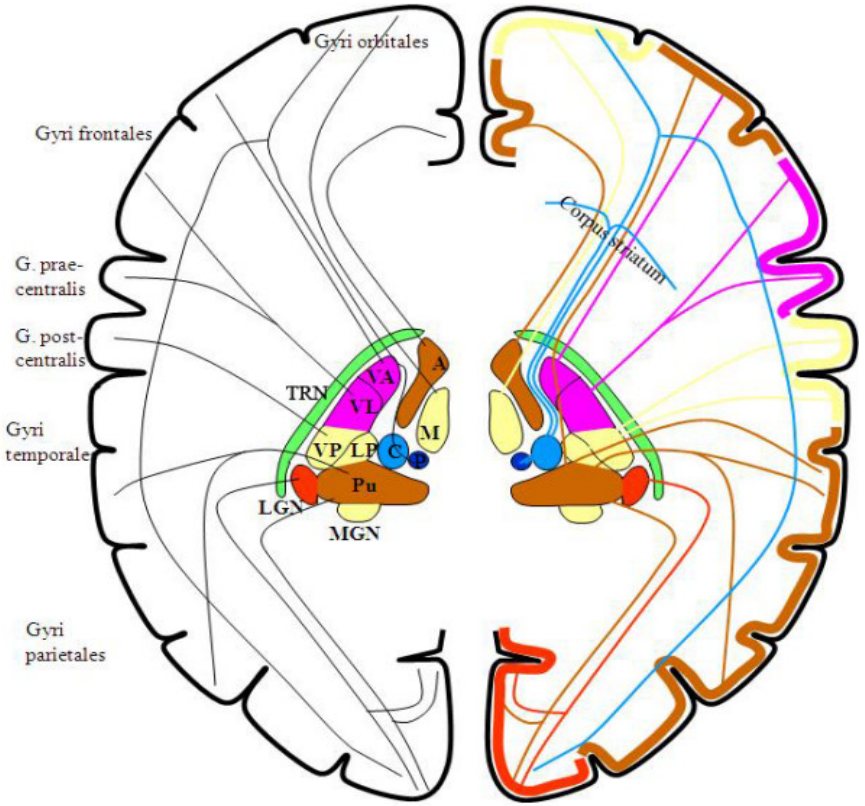
Key Factors for Cassette Design & Optimization

- Potency of knockdown
- Guide:passenger ratio
- Precision of guide strand processing
- Candidate miRNA level relative to endogenous pool

Putamen and Thalamus Route of Delivery

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

Cortical → thalamic connections

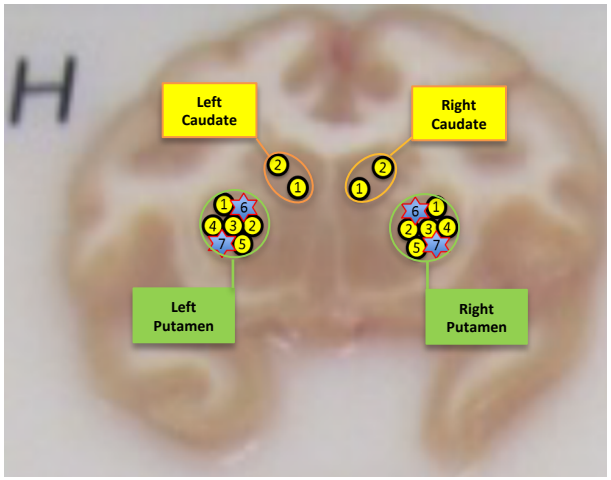


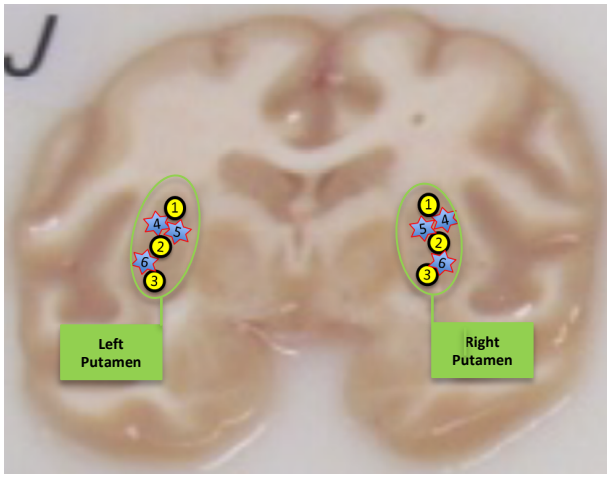
Thalamic → cortical connections

Source: Min 2010, Theor Biol Med Model

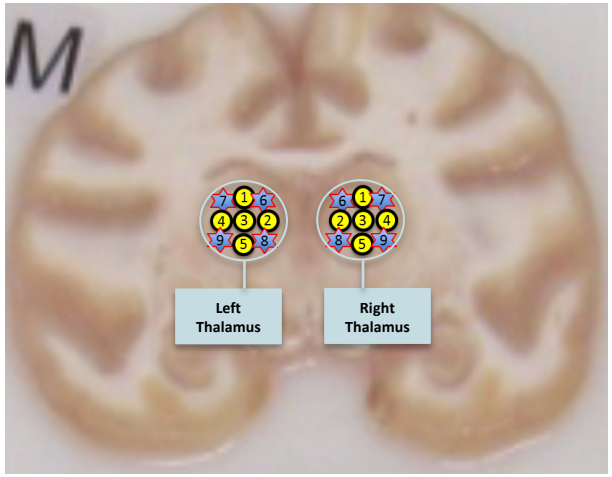
Brain Tissue Punch and Laser-Capture Locations

Striatum (Putamen and Caudate)



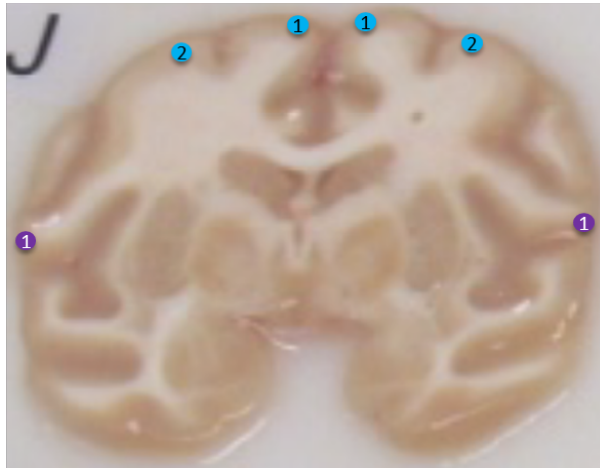


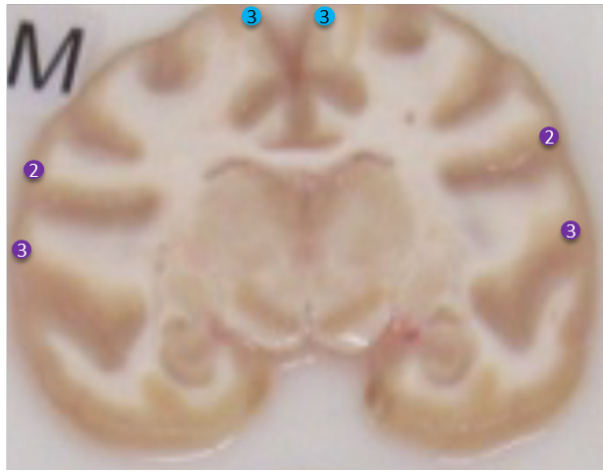
Thalamus



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

Cortex (Laser Captured Neurons)



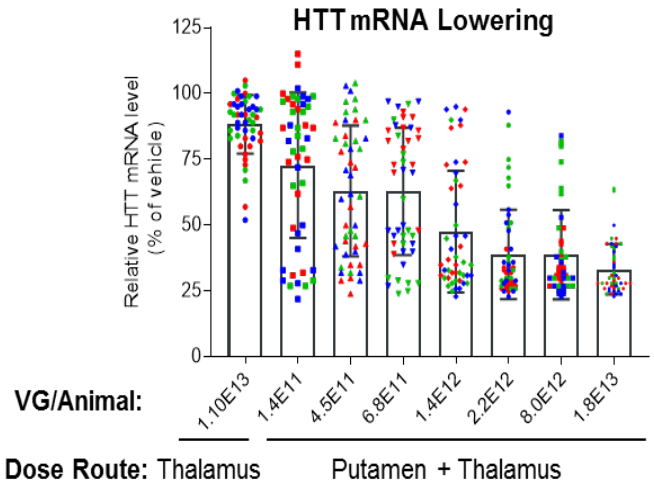


Source: ESGCT 2018 Poster P190

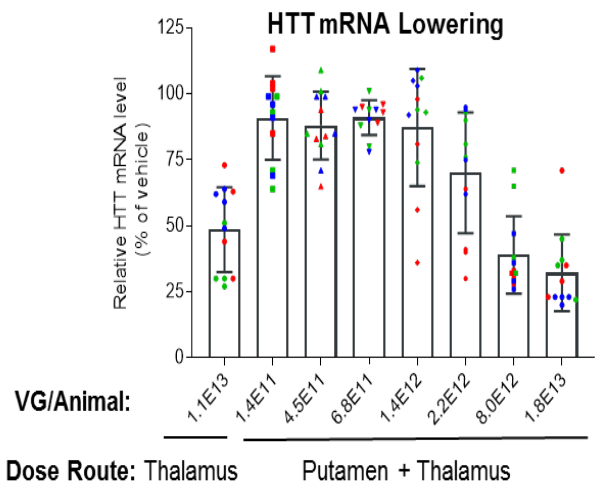
Robust HTT mRNA Lowering in Adult NHPs

Putamen (67%), Caudate (68%), and Cortical Neuron (32%) HTT mRNA Lowering [1]

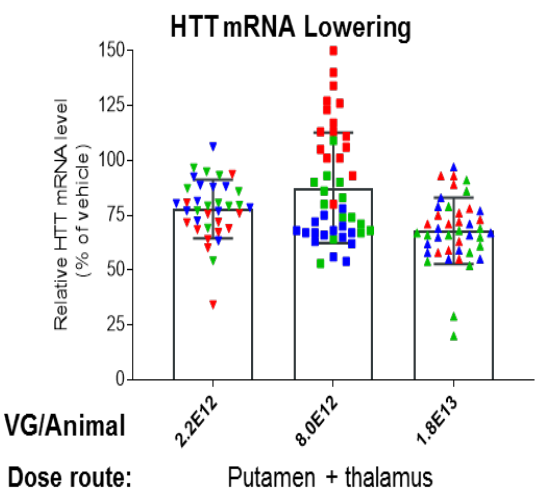
Putamen



Caudate



Cortical Neurons



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

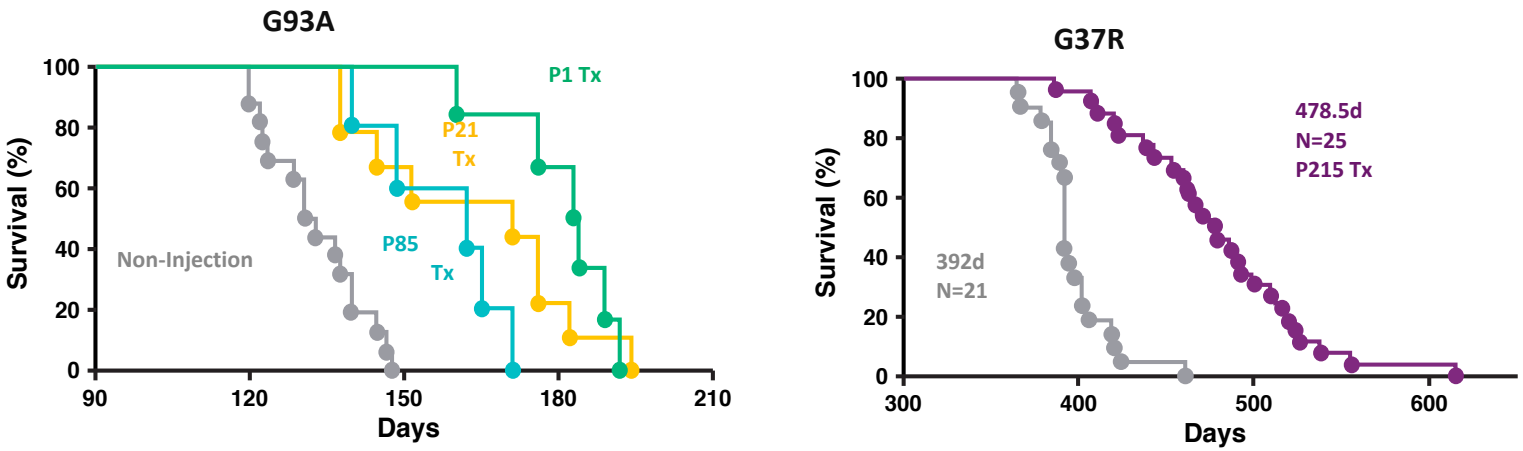
Mutant SOD1 is associated with disease:

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

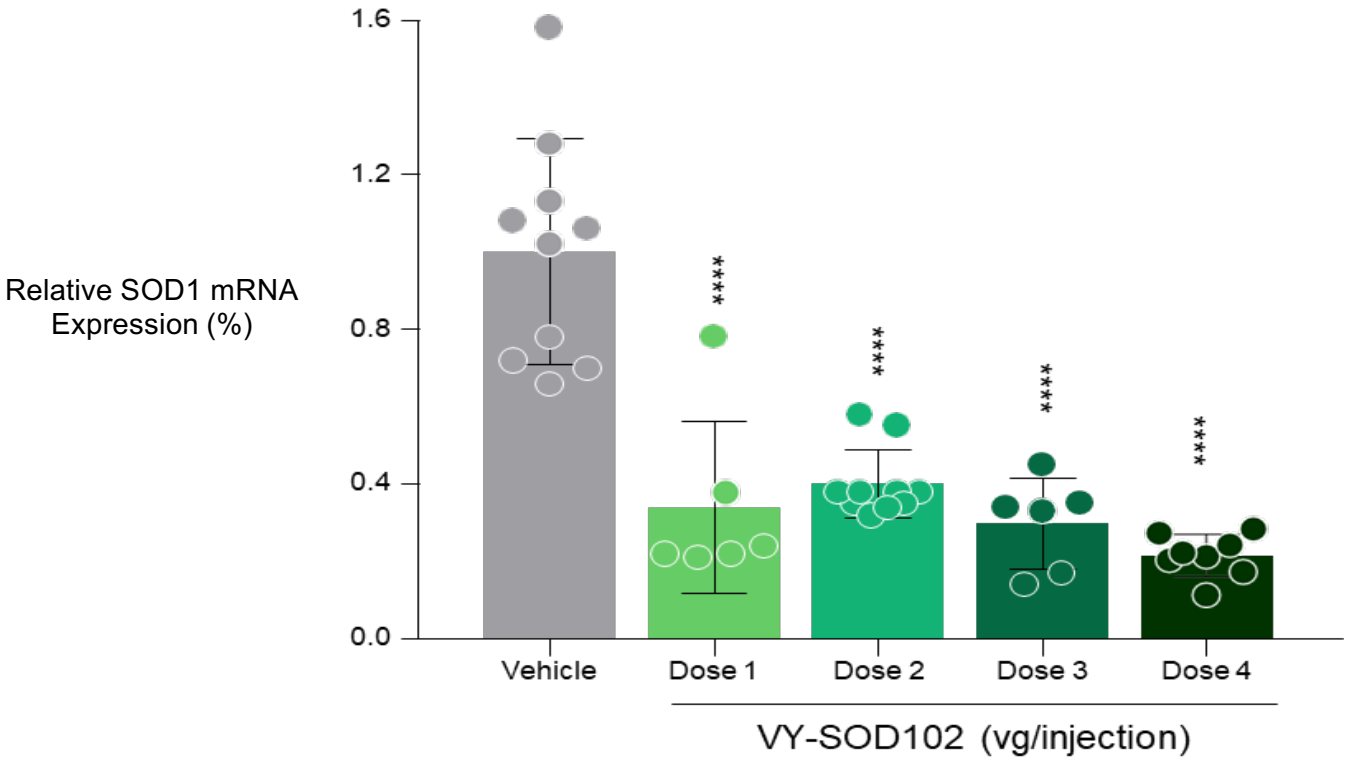
IV AAV9-shSOD1 Extends Survival of ALS Mouse Model



Source: Foust et al., 2013

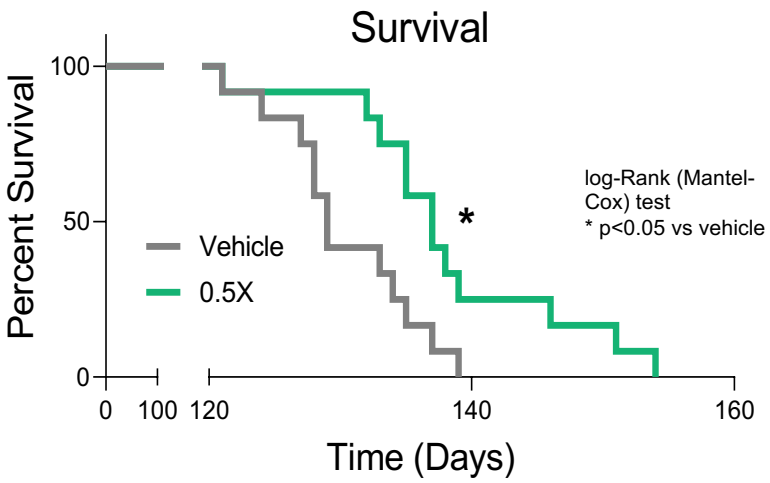
VY-SOD102: Robust Reduction of Human SOD1 in Transgenic Mice

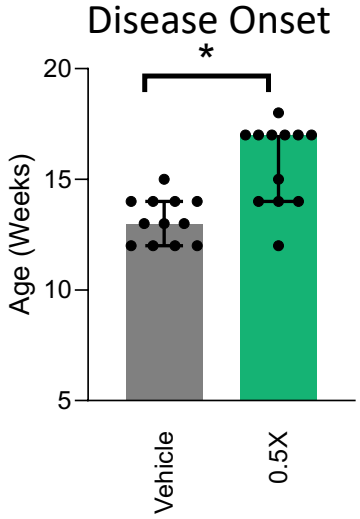
Significant mRNA SOD1 reduction 4-weeks post intrastriatal dosing

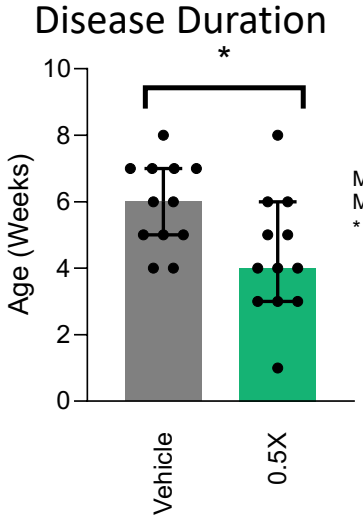


Source: ESGCT 2018 Poster P185

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







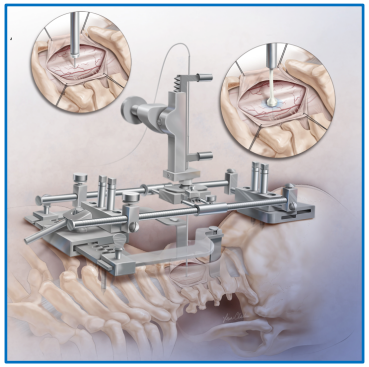
Source: ASGCT 2019
Bilateral intra-lumbar spinal cord delivery

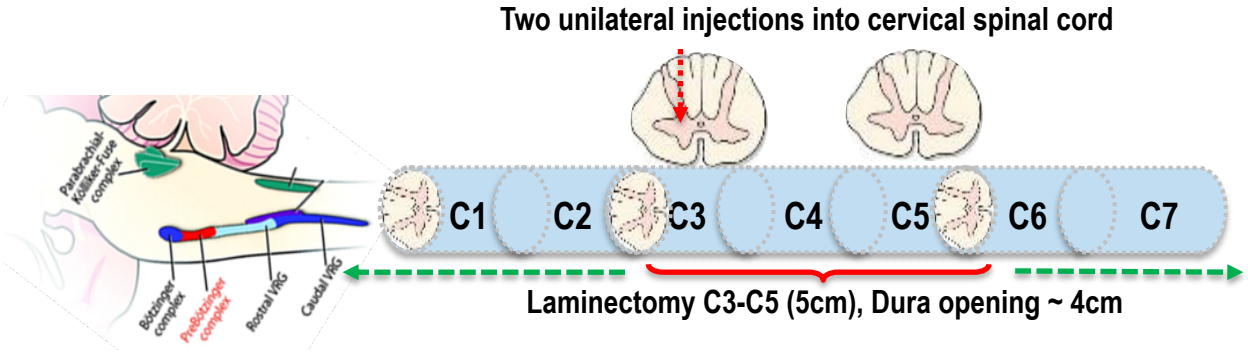
VY-SOD102: Novel Delivery Paradigm

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

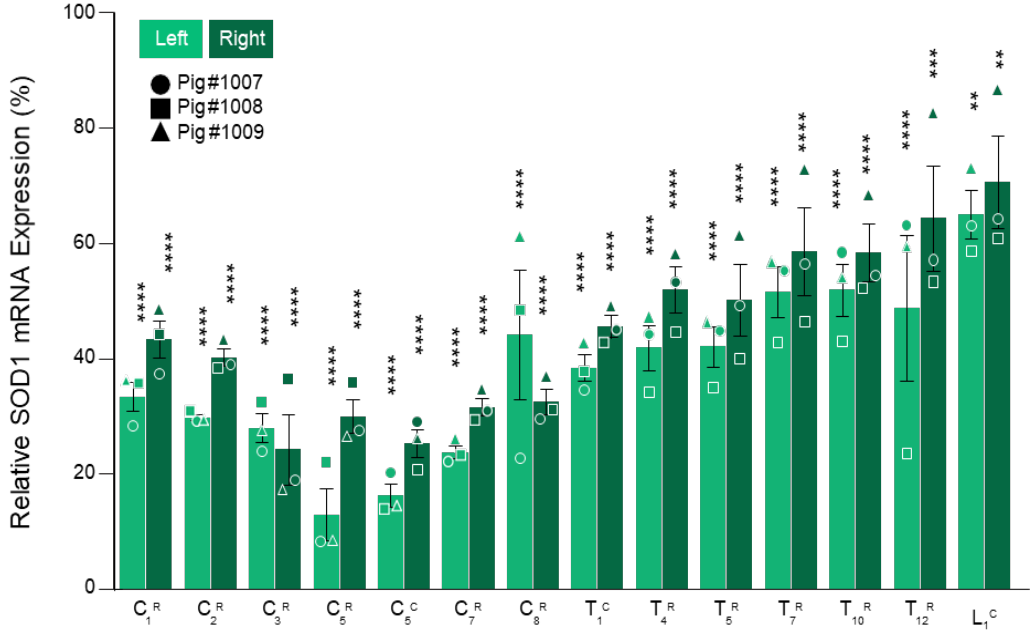




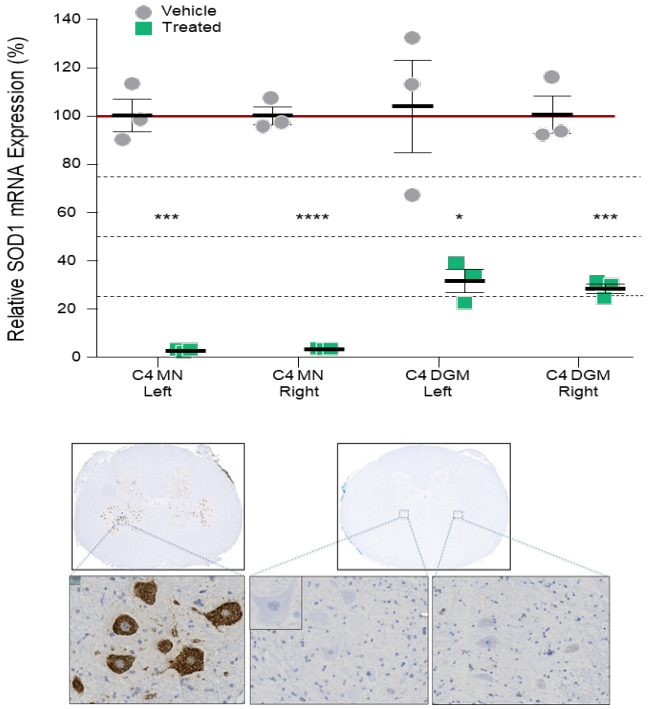
Source: ESGCT 2018 Poster P185

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:



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)

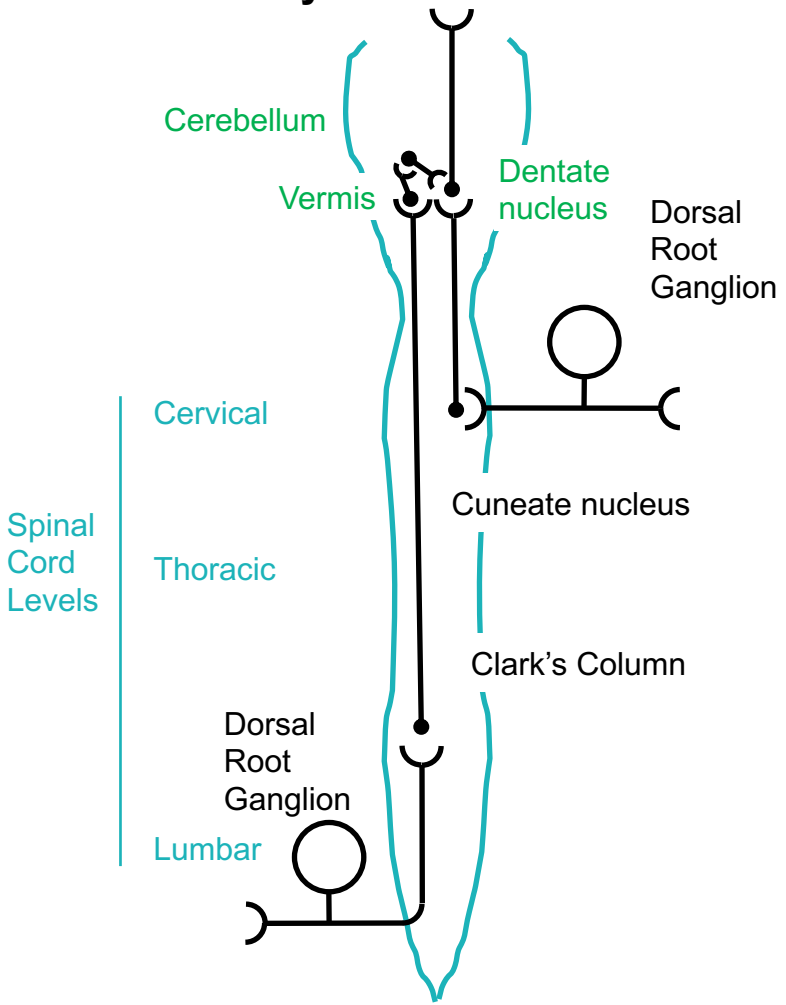
Fatal, debilitating neurodegenerative and cardiac disease affecting ~6,400 patients in the US:

- 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

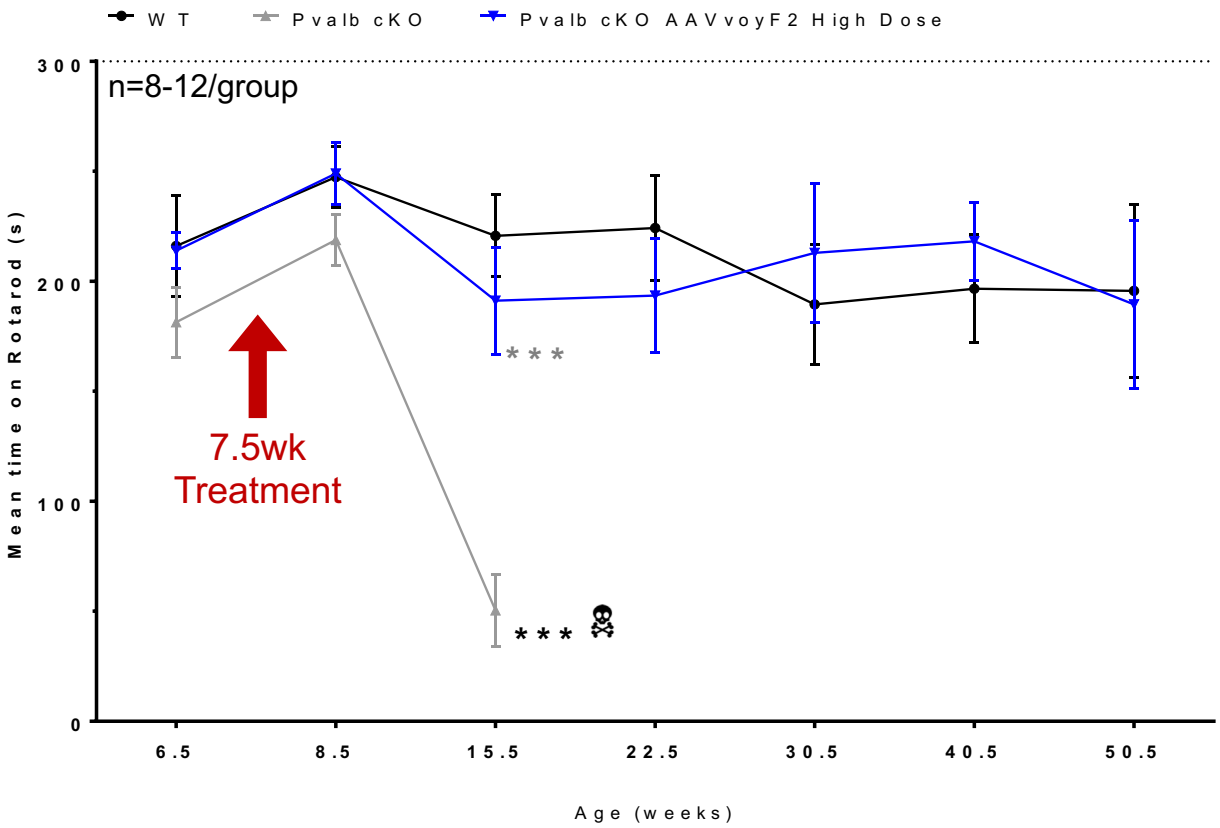
Goal

- 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



*, **, *** p < 0.05, 0.01, 0.001 vs respective color, one-way ANOVA followed by Tukey's post hoc test.
A T-test was used to compare AAVvoyF2 treated animals and WT after 15.5 weeks of age.

- 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:

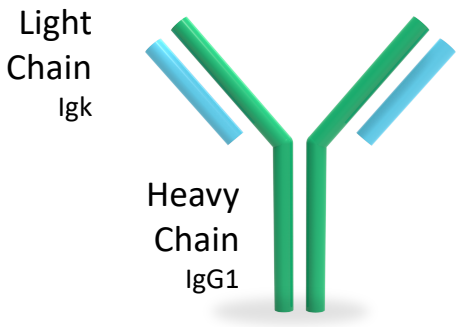
- In tauopathies, tau aggregates and becomes hyper-phosphorylated, forming insoluble tau-containing neurofibrillary tangles
- The progressive spread of tau pathology along distinct anatomical pathways in the brain closely correlates with disease progression and severity in a number of tauopathies, including 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

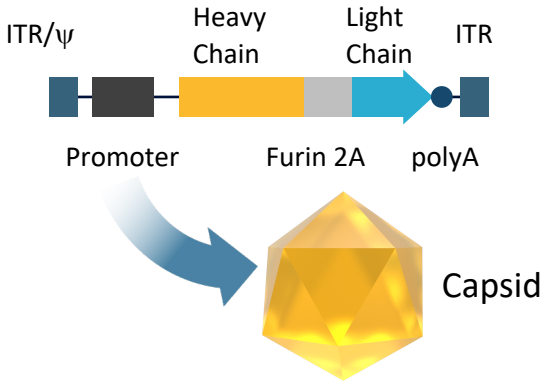
Goal:

- *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

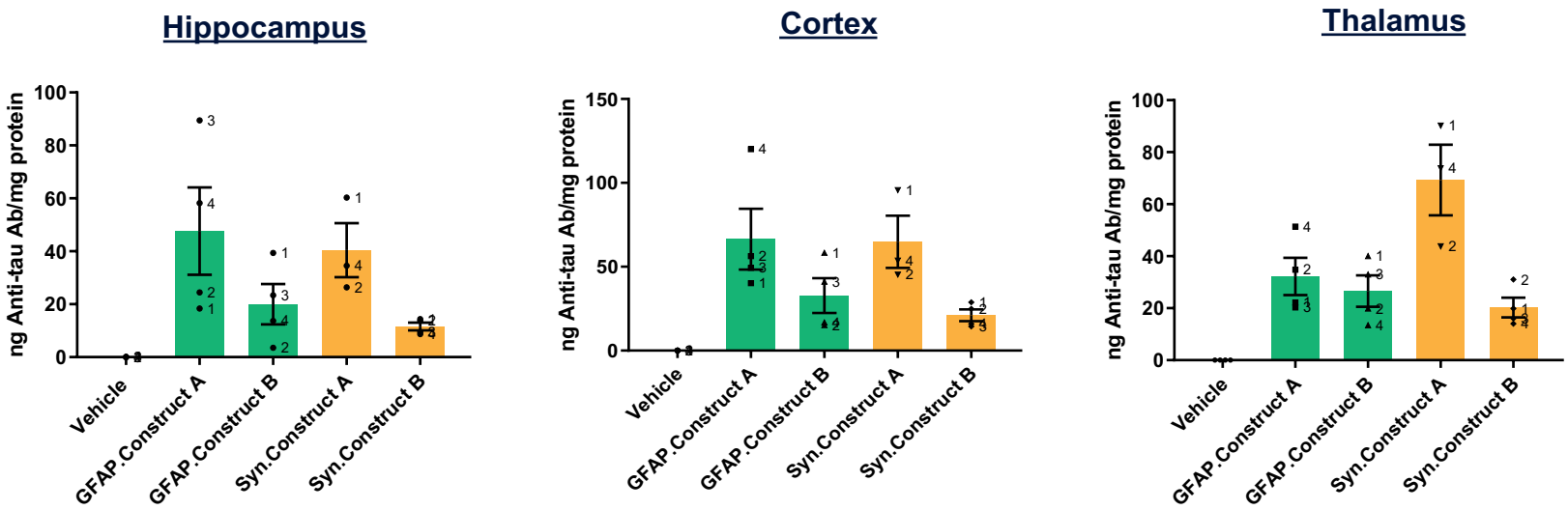
Components for Optimization

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[1]



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