
Voyager®
THERAPEUTICS
Developing Life-Changing Therapies for
Severe Neurological Diseases
June 2020

Forward-Looking Statements

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Building a Leading Neuro Gene Therapy Company

AAV Gene Therapy

Voyager Therapeutics is at the intersection of gene therapy and the central nervous system

Severe Neurological Diseases

Developing **life-changing AAV gene therapies** for people living with **severe neurological diseases**

Lead program, VY-AADC (NBIb-1817) in Parkinson's disease in pivotal trial; **long-term Phase 1 data expected in 2H 2020**

Balanced pipeline of wholly owned and partnered programs; **validating partnerships** with Neurocrine Biosciences and Abbvie

Unique approach leveraging three therapeutic modalities to enable expanded targeting of neurological diseases

Extensive expertise in AAV vector engineering & optimization, manufacturing and delivery techniques

Leveraging Three Distinct Therapeutic Modalities

Three-pronged approach to developing gene therapies allows for addressing an expanded pipeline of neurological diseases

1

Gene Replacement

Parkinson's Disease

Friedreich's Ataxia

2

Gene Knockdown

Huntington's Disease

Monogenic ALS

3

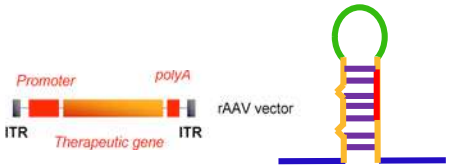
Vectorized Antibodies

Tauopathies
(Alzheimer's, PSP, FTD)

Synucleinopathies
(Parkinson's, LBD, MSA)

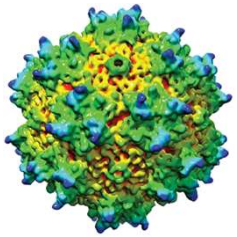
Undisclosed early pipeline programs across all modalities

Gene Therapy Development Requires Multiple Optimizations



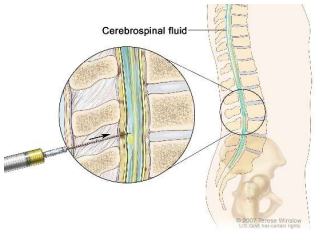
Vector Genome Design

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



AAV Capsid Selection

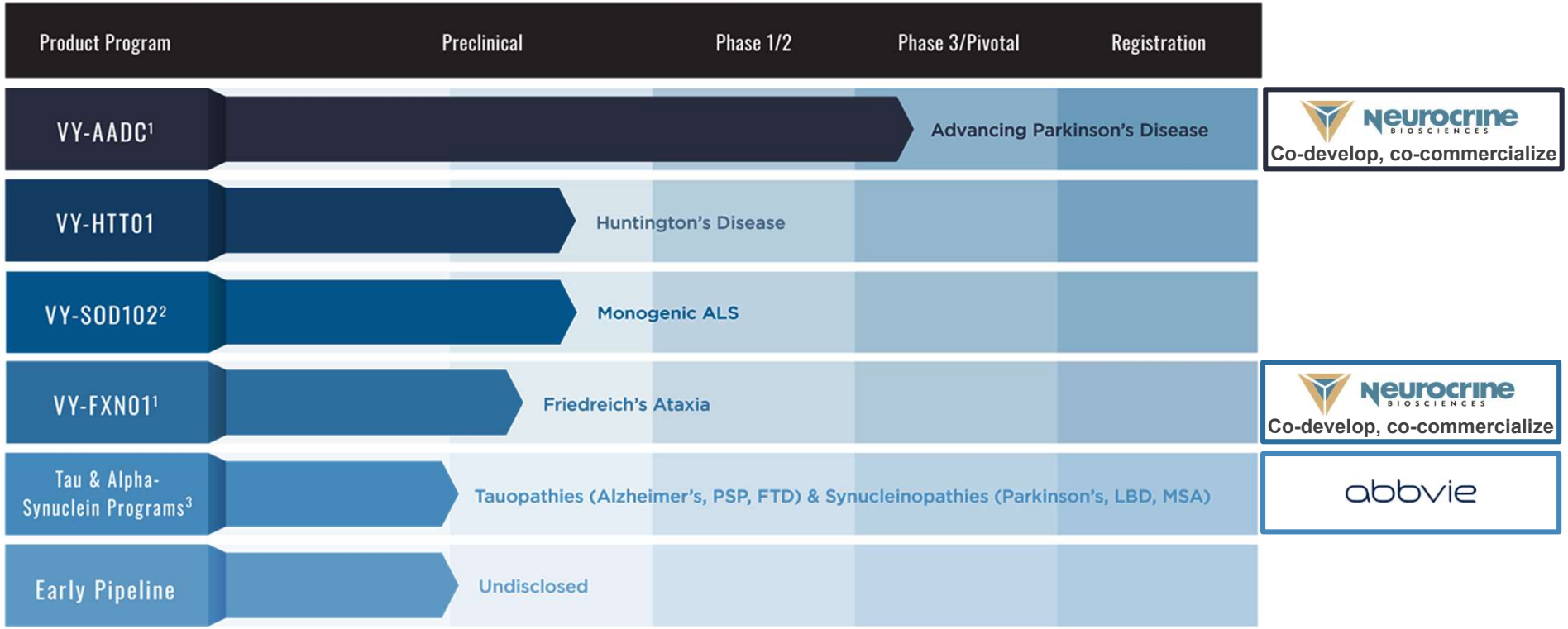
Tropism for relevant tissue and cell types



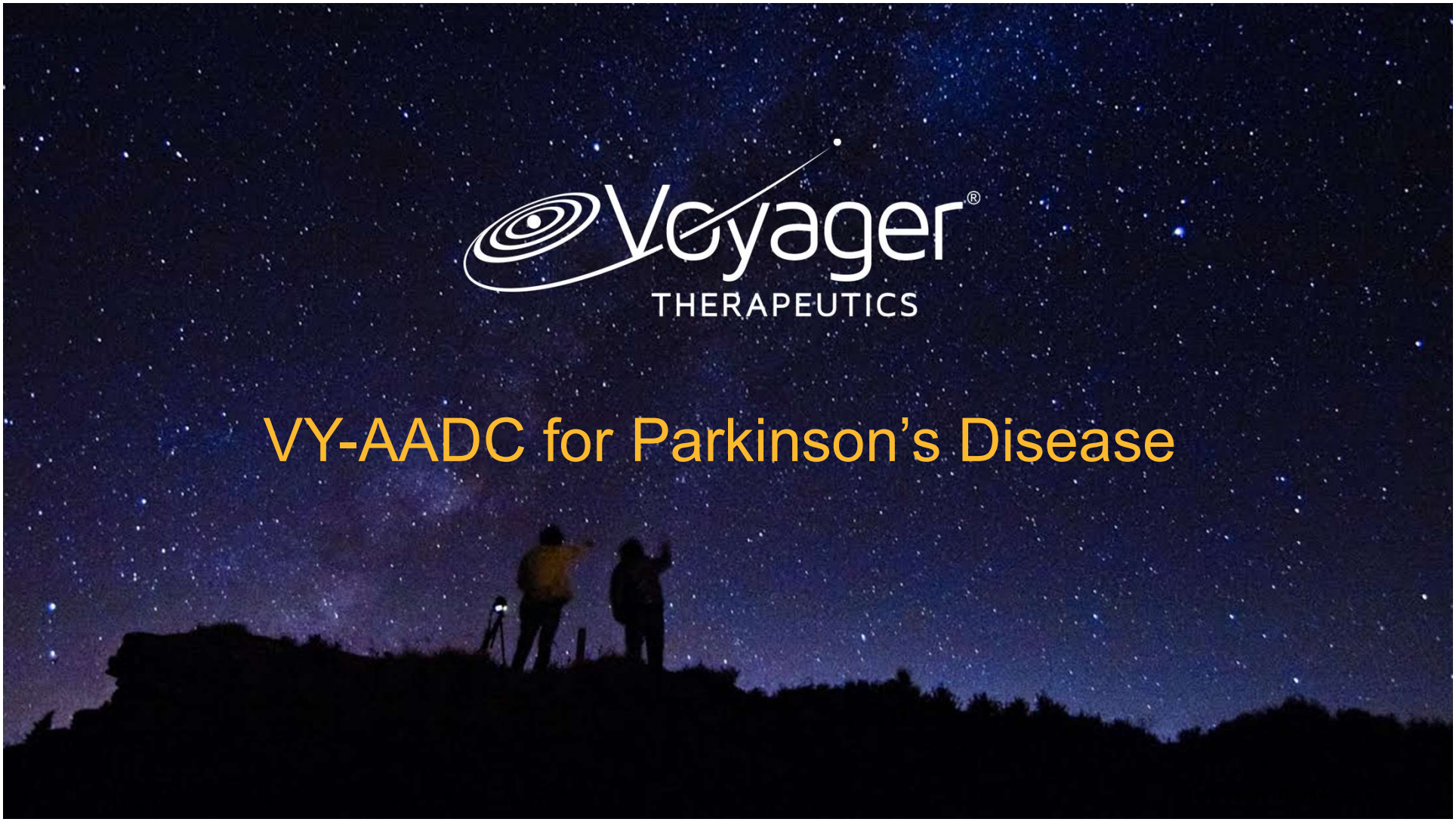
Delivery Optimization

Translatable dosing paradigm that provides target distribution profile in relevant tissues

Focused on Severe Neurological Diseases



(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, LBD = Lewy Body Dementia, MSA = Multiple System Atrophy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VY-AADC for Parkinson's Disease

Parkinson's Disease: ~1 Million Underserved Patients in the U.S.

Overview

- 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
- Current treatment standard still has significant limitations

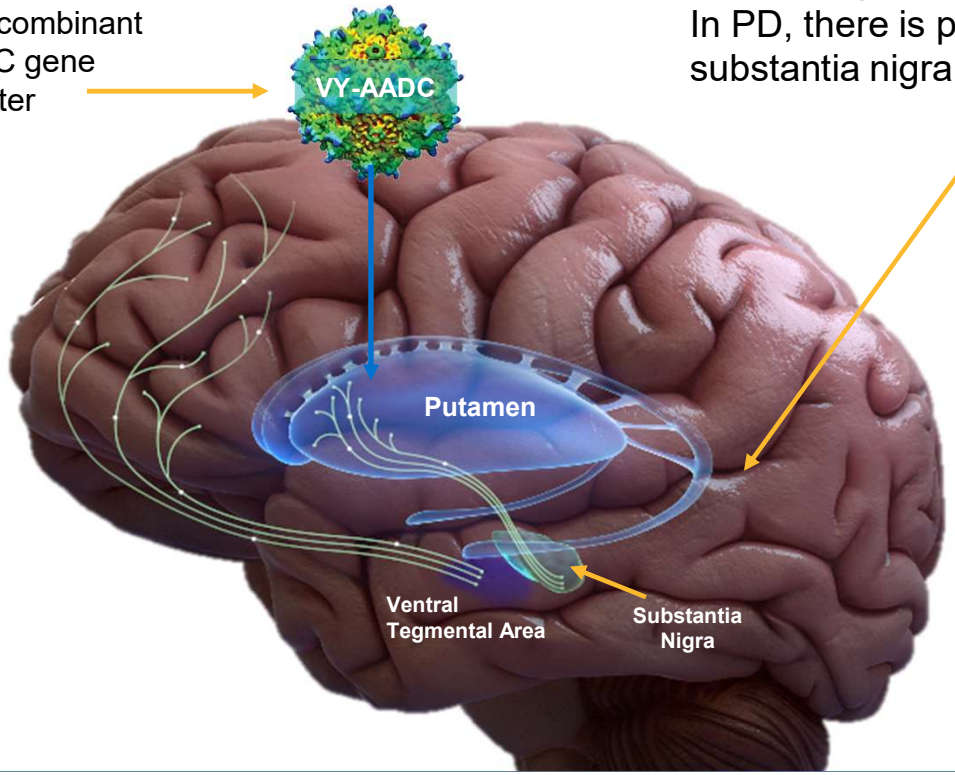
Voyager Clinical Development

- RESTORE-1 pivotal trial (in collaboration with Neurocrine)
- 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

VY-AADC Aims to Restore AADC Enzyme Activity

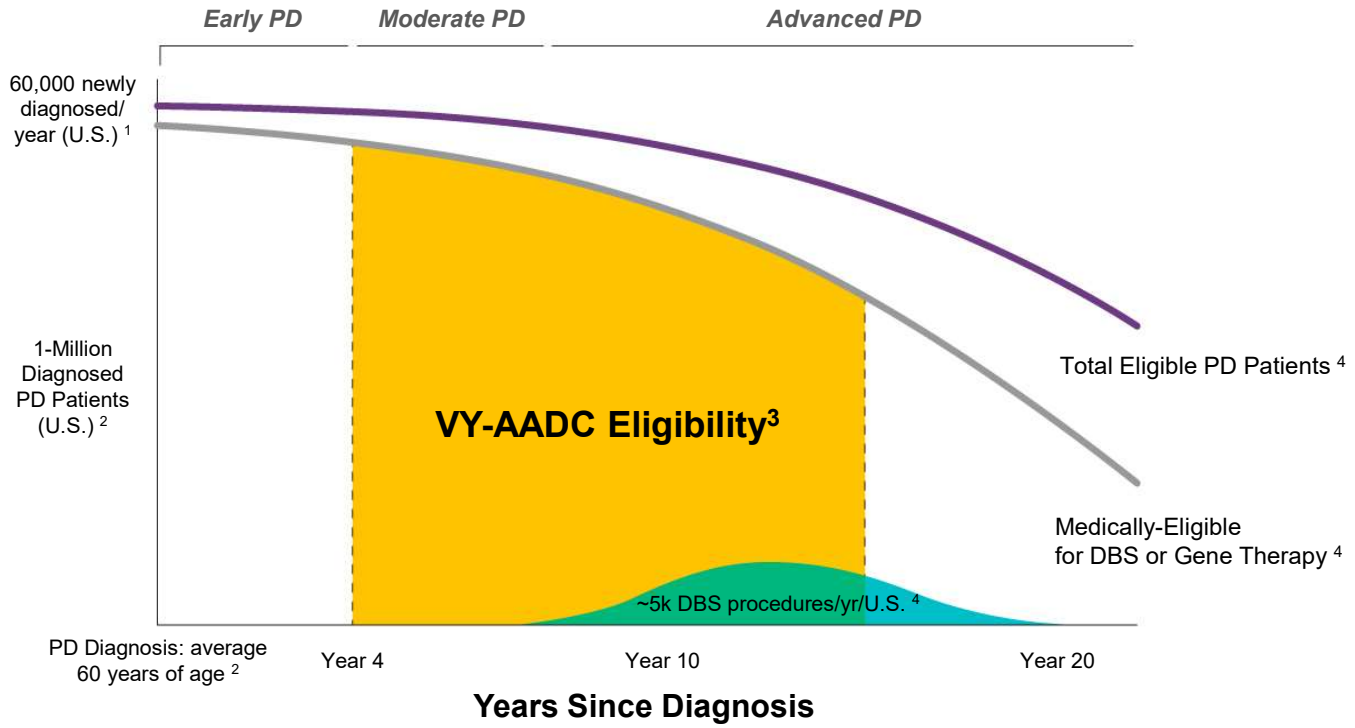
- AAV-2 Capsid/Recombinant
- cDNA of the AADC gene
- CMV early promoter



The Ability to Make AADC is Lost as PD Advances
In PD, there is progressive loss of fibers from the substantia nigra to the putamen

Approach: Introduce AADC to Healthy Postsynaptic Neurons in the Putamen
to replace degrading enzyme, improve levodopa sensitivity, and potentially improve clinical motor function

VY-AADC: Parkinson's Disease Patient Eligibility

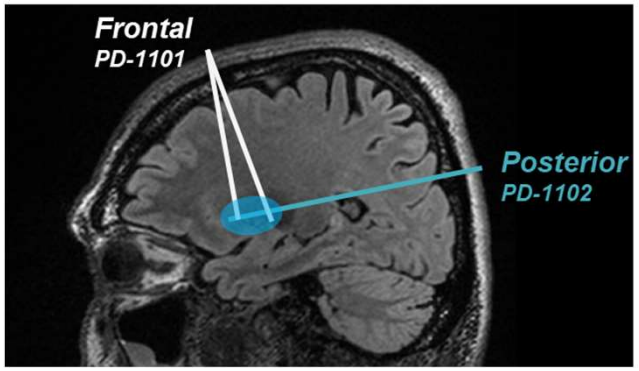


(1) Parkinson.org (2) Michael J. Fox Foundation (3) VY-AADC Phase 2 eligibility > 4 years since diagnosis > 3 hours diary OFF time (4) Voyager estimates

Phase 1 Program to Optimize Dosing and Delivery

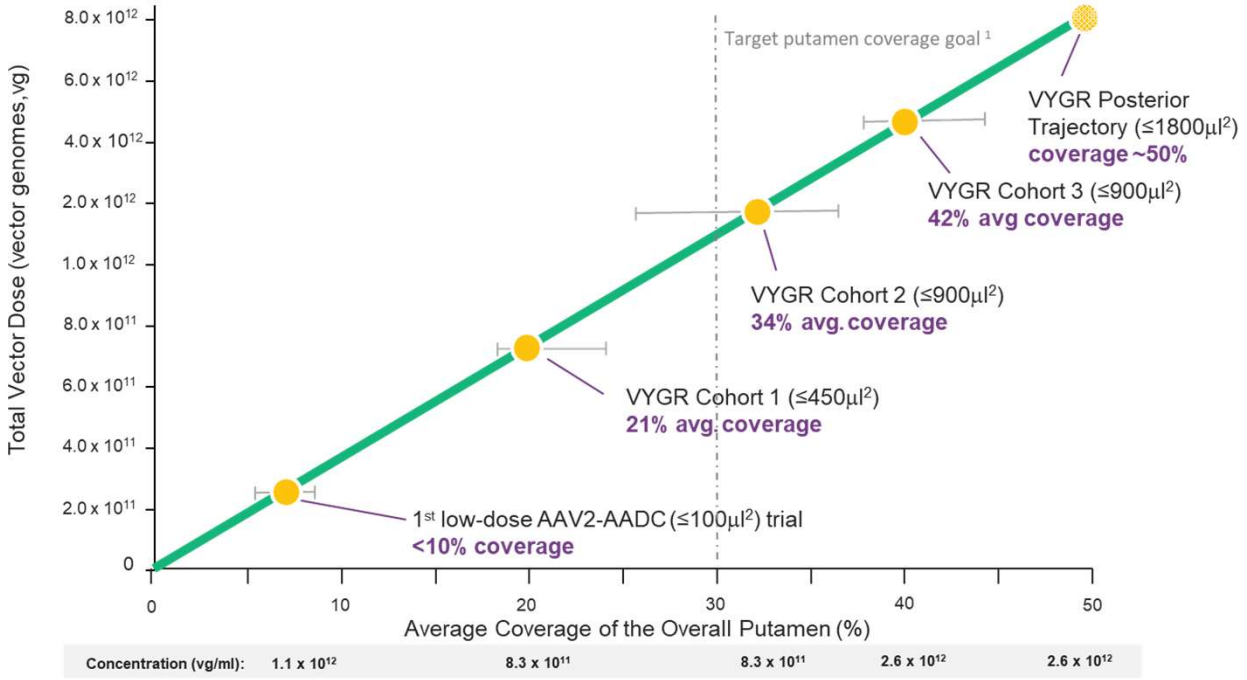
PD-1101: Two or more trajectories per putamen with frontal approach

PD-1102: One trajectory per putamen with posterior approach



Study and Cohort	N	Volume per Putamen	Concentration	Total Dose
PD-1101 cohort 1	5	Up to 450 µL	8.3×10^{11} vg/mL	Up to 7.5×10^{11} vg
PD-1101 cohort 2	5	Up to 900 µL	8.3×10^{11} vg/mL	Up to 1.5×10^{12} vg
PD-1101 cohort 3	5	Up to 900 µL	2.6×10^{12} vg/mL	Up to 4.7×10^{12} vg
PD-1102	8	Up to 1800 µL	2.6×10^{12} vg/mL	Up to 9.4×10^{12} vg

Phase 1 Dose Escalation and Putamen Coverage



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

VY-AADC Phase 1 Baseline Characteristics

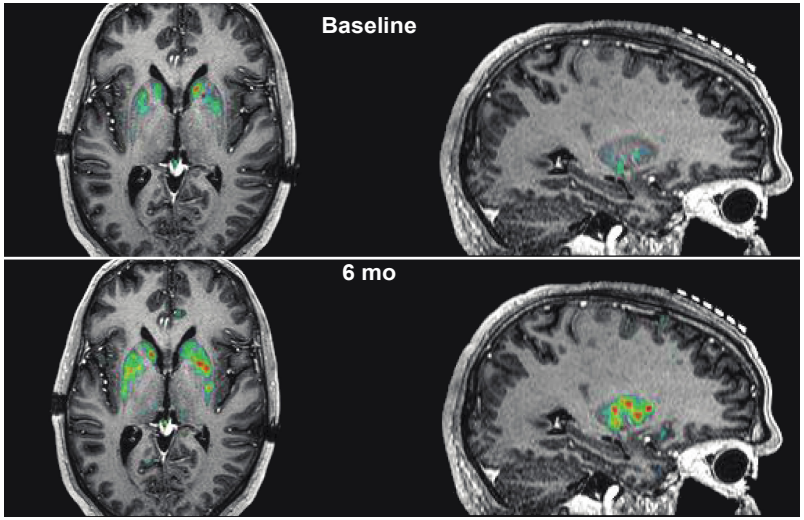
	PD-1101 Cohort 1	PD-1101 Cohort 2	PD-1102 Cohort 3	PD-1102
Age	57.4 (7.2)	58.4 (8.6)	57.4 (4.5)	56.8 (11.0)
Sex	1 Female, 4 Male	5 Male	1 Female, 4 Male	1 Female, 7 Male
PD Duration (years)	9.9 (4.6)	10.1 (1.6)	8.5 (3.6)	9.2 (5.9)
UPDRS II off	13.6 (2.1)	16.0 (1.7)	19.8 (7.8)	15.3 (5.9)
UPDRS II on	3.0 (2.9)	3.6 (1.7)	5.0 (3.9)	3.5 (4.3)
UPDRS III off	37.2 (5.9)	35.8 (7.6)	38.2 (9.7)	34.9 (5.2)
UPDRS III on	7.6 (5.1)	17.0 (3.8)	16.0 (3.1)	11.4 (5.9)
Diary off-time (hrs)	4.9 (1.7)	4.2 (1.4)	4.7 (1.2)	6.8 (1.6)
Diary on-time (hrs)	10.5 (2.1)	10.7 (1.8)	10.3 (1.6)	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 (13.7)
LED(1) mg	1467.5 (615.0)	1635.5 (687.3)	1476.5 (429.1)	1557.1 (507.6)

(1) Levodopa Equivalent Dose
Mean (standard deviation)

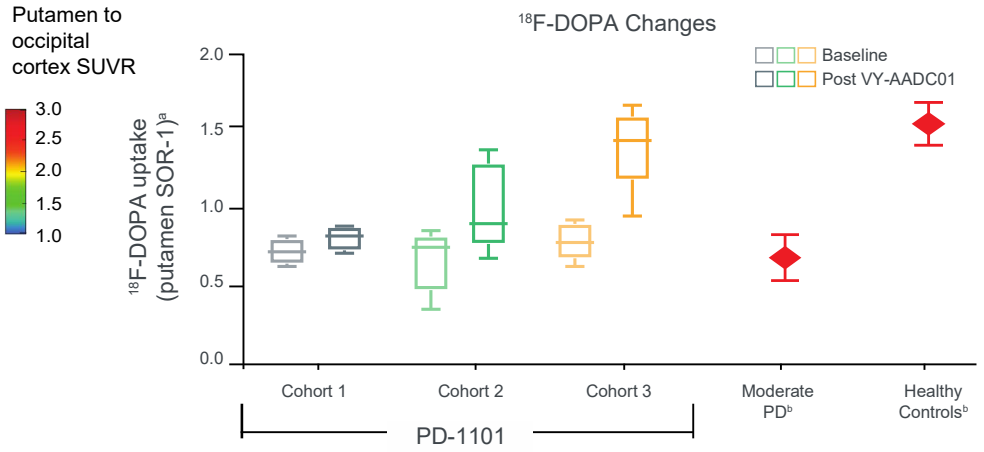
Source: Voyager Therapeutics and Christine, C. W., et al., (2019), Ann Neurol. doi:10.1002/ana.25450

Demonstrated Improvements to AADC in Phase 1 Studies

PD-1101: Increased AADC Enzyme Activity Detected by PET Imaging and F-Dopa Uptake



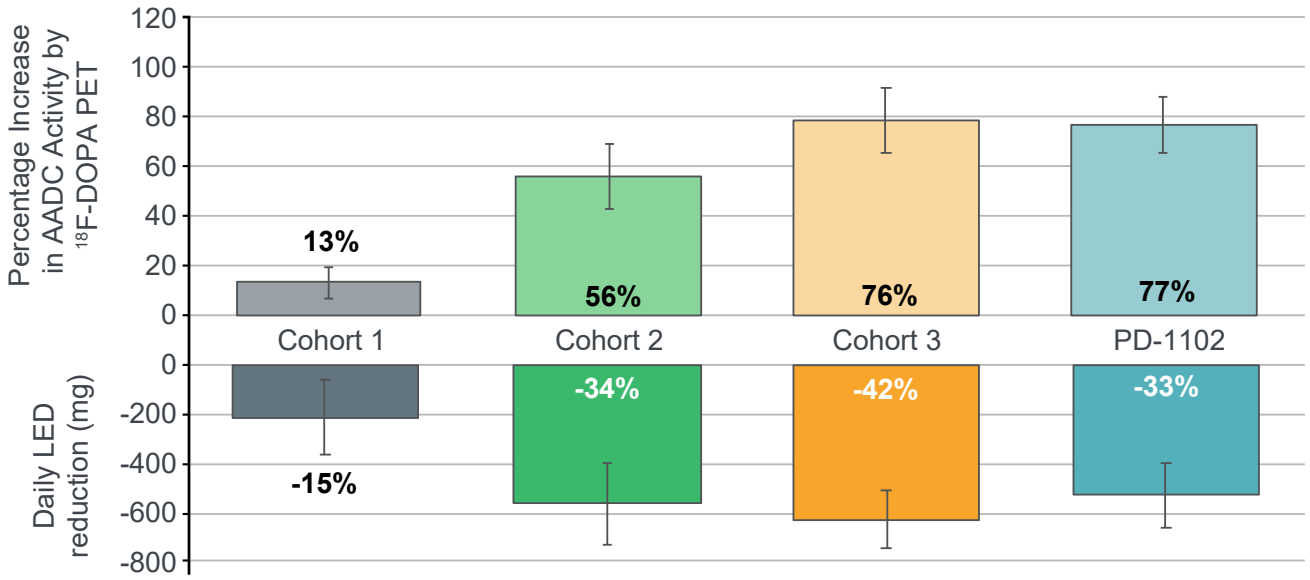
PET, Positron Emission Tomography



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



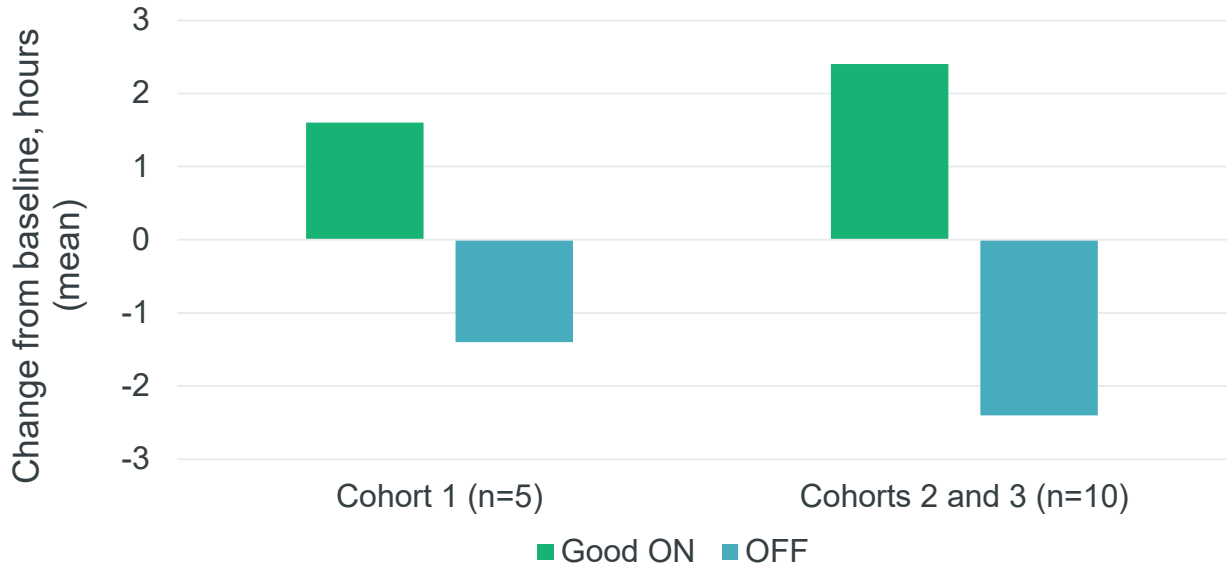
Reductions in LED (Levodopa Equivalent Dose) sustained at higher dose cohorts:

- 21% reduction for Cohort 2 at 2 years
- 43% reduction for Cohort 3 at 18-months

Source: Voyager Therapeutics

Clinically Meaningful Improvements Demonstrated in Phase 1

Improvement in Good ON time (primary endpoint in pivotal trials) and reduction in OFF time at 12 months

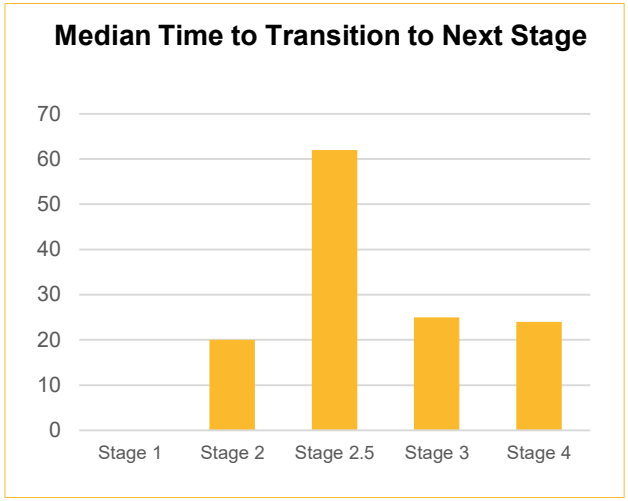


Source: Voyager Therapeutics press release 11/7/18

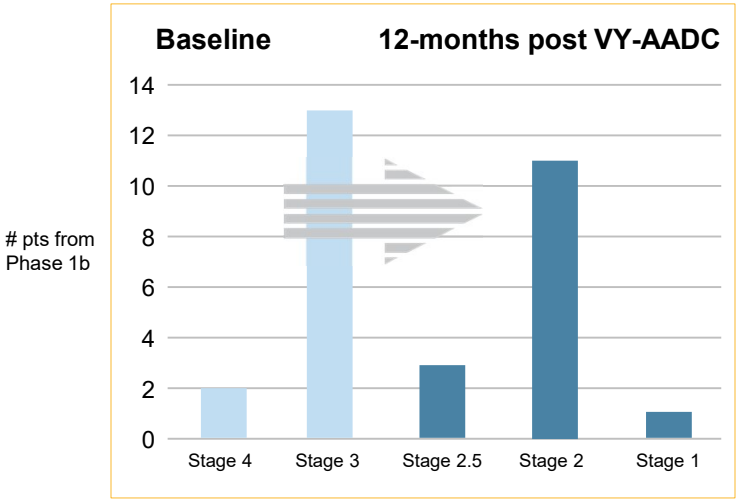
VY-AADC Phase 1: Shift in Disease Staging

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

PD-1101: Safety Summary

- Surgical procedure successfully completed in all 15 patients
- Infusions of VY-AADC have been well-tolerated with no vector-related serious adverse events (SAEs)
- 14 of 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

RESTORE-1: First Pivotal Trial of VY-AADC

Randomized, double-blind, placebo-controlled trials evaluating the safety and efficacy of VY-AADC for the treatment of Parkinson's disease in ~85 patients (randomized 2:1)

Dose

Total dose of up to 2.5×10^{12} vector genomes

Primary endpoint

ON time without troublesome dyskinesia, or good ON time, as measured by a self-reported patient diary at 12 months.

Biomarker data

VY-AADC putaminal coverage, AADC enzyme expression and activity by PET

Inclusion criteria

- PD diagnosis $\geq$ 4 yrs
- 3 hours of OFF time
- Not responding adequately to oral medications

Secondary endpoints

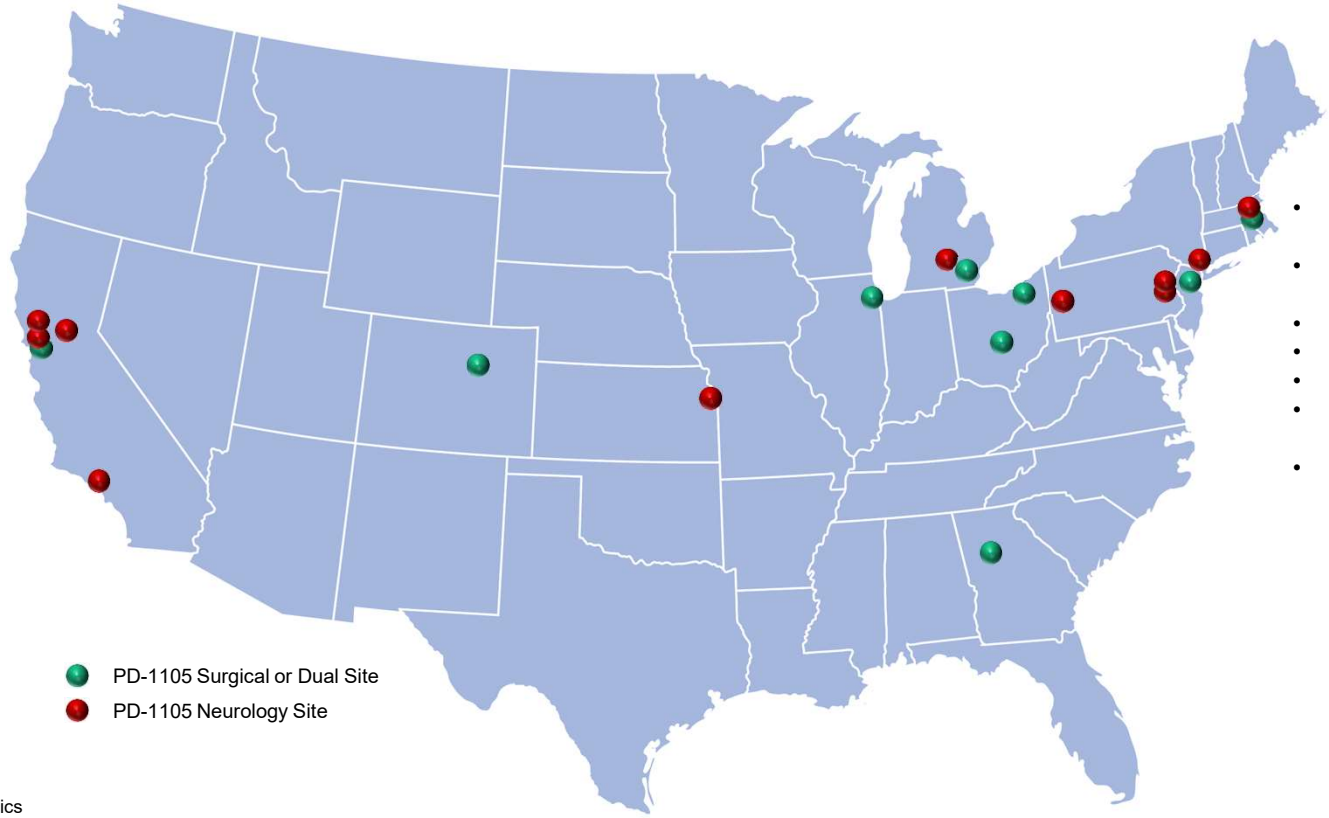
- Diary OFF time
- Changes in daily doses of oral levodopa
- Other motor function and quality of life measures from the UPDRS-II,-III scores, the PDQ-39, and PGI and CGI scores.

RESTORE-1 Trial Sites at Top Academic Centers

Over 20 Surgical and Neuro Sites

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

- University of California, San Francisco
- San Francisco VA Medical Center
- 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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VY-HTT01 for Huntington’s Disease

Huntington's Disease: ~30,000 Patients in the U.S.

Overview

- 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

Voyager Clinical Development

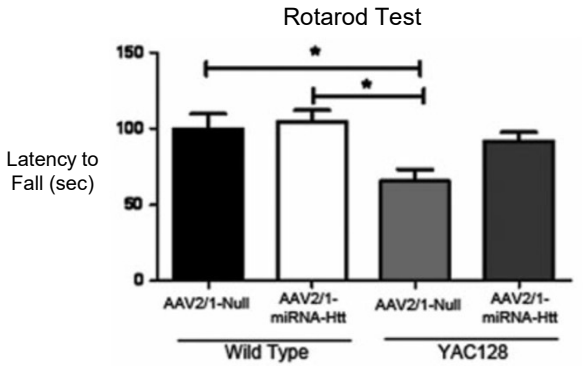
- VY-HTT01: anti-HTT RNAi gene therapy to knockdown HTT mRNA in striatum and cortex to slow disease progression
- VY-HTT01 in IND-enabling studies

AAV Gene Therapy Rationale for Lowering HTT

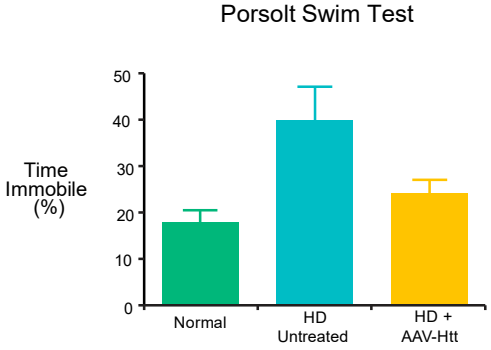
- Mutant huntingtin is causal for disease and has numerous deleterious molecular and cellular effects
- Transgenic models confirm pathogenicity of poly-Q HTT
- RNAi or ASO studies in HD animal models demonstrate that partial lowering of HTT provides potential therapeutic benefit and is well-tolerated

> 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)



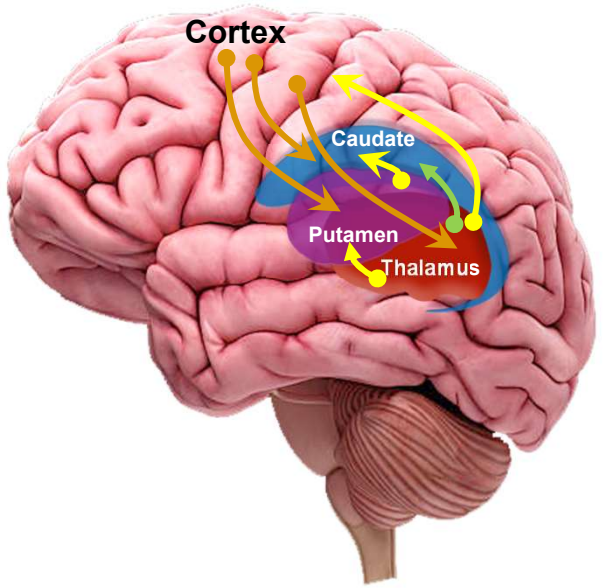
Source: Stanek et al., 2014

Putamen and Thalamus Route of Delivery Leverages Rich Connections

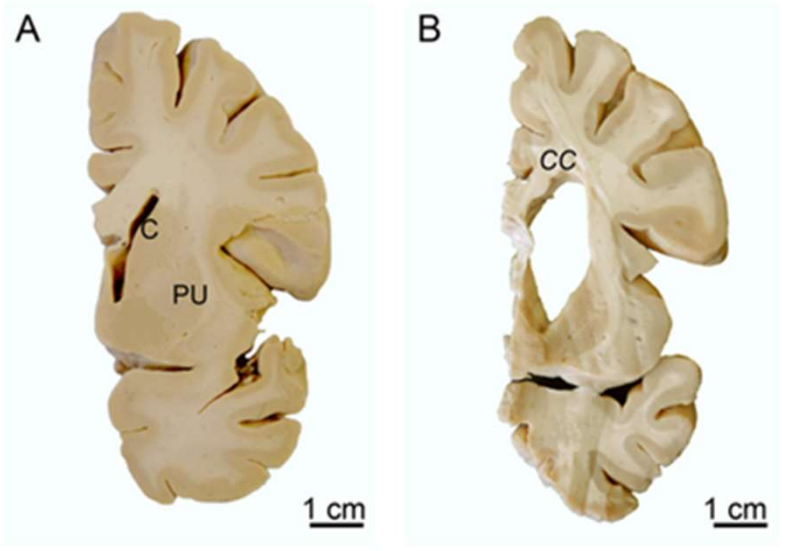
Putamen and thalamus delivery leverages more extensive and preserved neuronal pathways to the cortex than delivery to the putamen alone

Targeting the thalamus:

- Extensive connectivity with the cortex and basal ganglia
- Preserved connectivity relative to the atrophic basal ganglia
- Relatively limited perivascular space enlargement
- Less challenging surgical trajectories

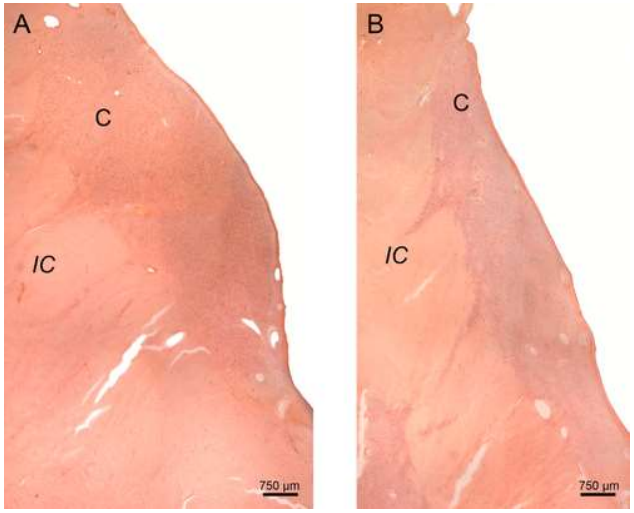


Huntington's Disease Brain Shows Significant Atrophy and Neuronal Loss in the Caudate



(A) Frontal section through the basal forebrain of a representative control individual caudate nucleus (C) and putamen (PU).

(B) Frontal section through the same basal forebrain level of a genetically confirmed Huntington's disease (HD) patient

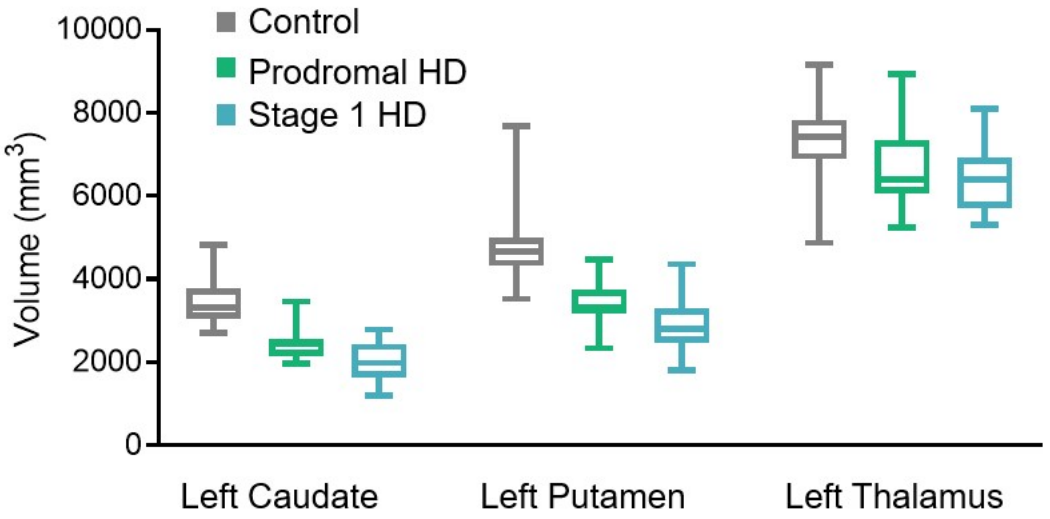


(A) Frontal section through the head of the caudate nucleus (C) of a representative control individual.

(B) Marked neuronal loss of the caudate of a representative Huntington's disease (HD) patient

Brain Pathology, Volume: 26, Issue: 6, Pages: 726-740, First published: 16 August 2016, DOI: (10.1111/bpa.12426)

Caudate and Putamen Show Significant Volume Loss
Impact Begins in Prodromal Stage

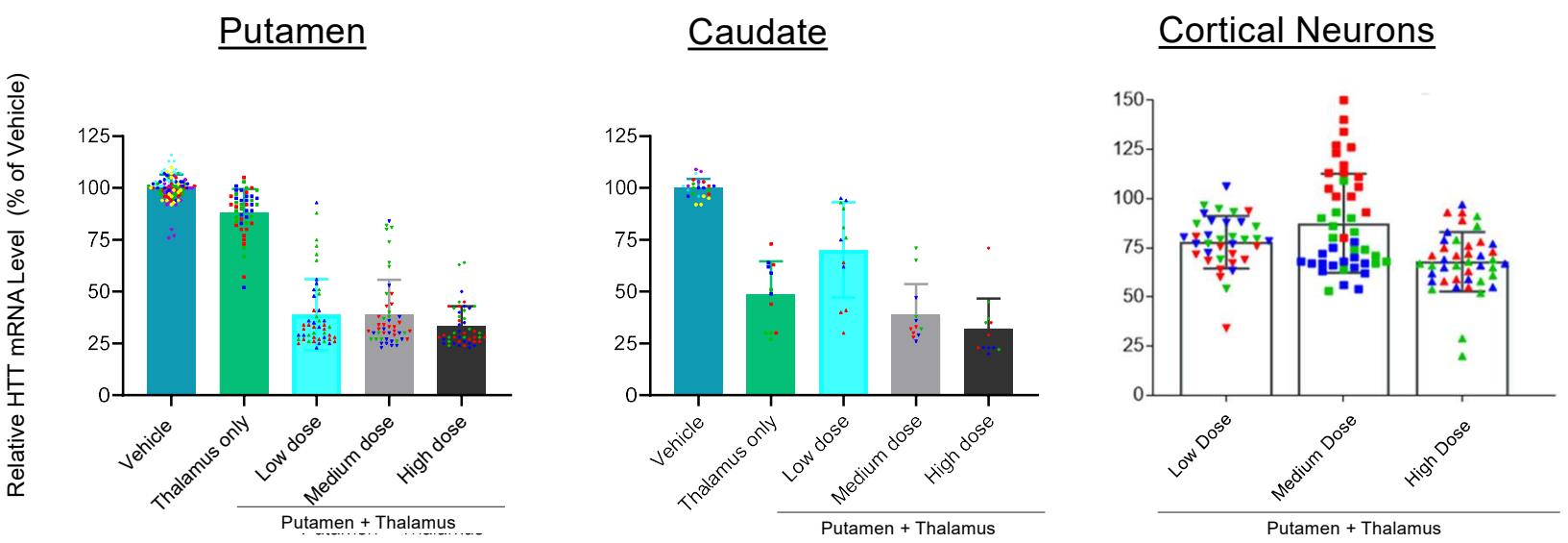


Wide range of structural sizes necessitates wide range of infusion volumes to achieve target coverage

Voyager data on file from study in collaboration with Massachusetts General Hospital. Box and whisker plot shows medians (central lines) 25th and 75th percentiles (boxes), and minima and maxima (bars).

Robust HTT mRNA Lowering in Adult NHPs at 5 Weeks

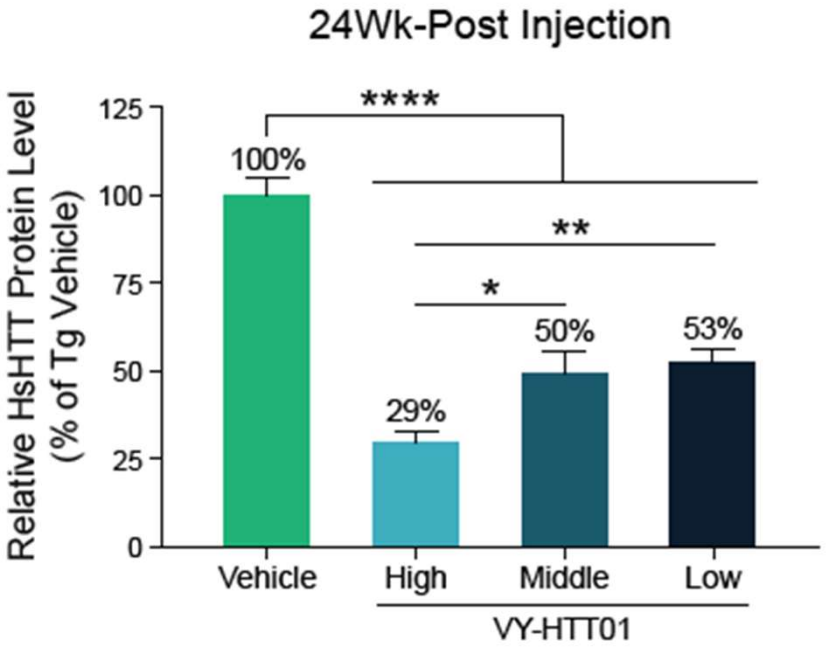
Putamen (67%), Caudate (68%), and Cortical Neuron (32%) HTT mRNA Lowering[1]



(1) Putamen and Caudate lowering measured from tissue punches; Cortical neuron lowering measured from laser-captured cortical neurons

Source: ESGCT 2018 Poster P190

Significant HTT Protein Knockdown in YAC128 Mice at 24 Weeks



* p < 0.05, ** p < 0.01, **** p < 0.0001

Source: CHDI 2020 Poster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Other Pipeline Programs

ALS: ~20,000 Patients in U.S.

Overview

- Rapidly progressive neurodegenerative disease with adult-onset resulting in severe muscle atrophy; usually fatal within 2-4 years of diagnosis
- Prevalence of SOD-1, a monogenic form of ALS: ~800 (U.S.)

Voyager Clinical Development

- VY-SOD102 targeting SOD-1 form of ALS currently in IND-enabling studies
- Partnership discussions ongoing for existing VY-SOD102 program as well as expanded ALS efforts (C9orf72, TDP43, etc.)

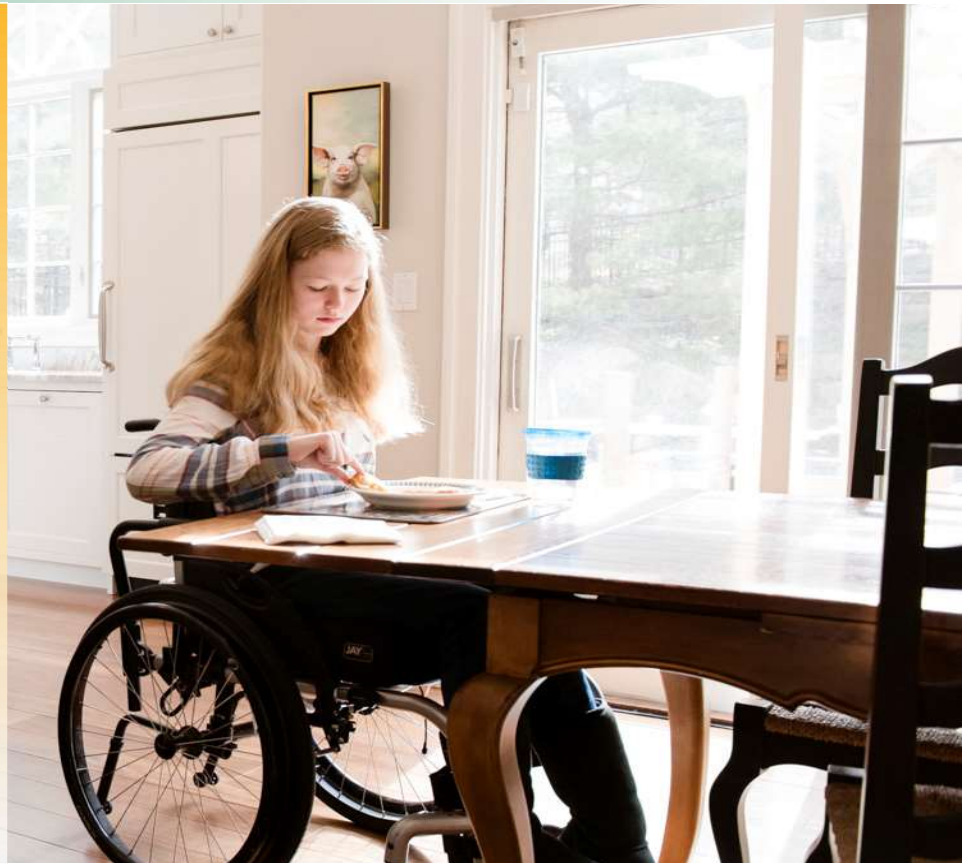
Friedreich's Ataxia: ~6,400 Patients in the U.S.

Overview

- 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 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

Voyager Clinical Development

- VY-FXN01 lead candidate selection ongoing in collaboration with Neurocrine



Vectorized Antibodies

Collaborations with AbbVie Targeting Tauopathies and Synucleinopathies

- Tau pathology is a hallmark of Alzheimer's disease, Frontotemporal dementia and Progressive Supranuclear Palsy, among others, and closely correlates with disease progression and cognitive decline
- Accumulation of misfolded alpha-synuclein can eventually lead to formation of protein deposits and progressive neurodegeneration in Parkinson's disease, and other synucleinopathies including Lewy Body Dementia and multiple system atrophy
- Vectorized antibody approach has potential for increased CNS levels of antibody versus passive immunization; potential for targeting intracellular aggregation, which passive immunization does not

Significant Progress Expected Across 2020

Program	Expected Milestone
VY-AADC for Parkinson's Disease	Present 3-year results from PD-1101 trial (2H 2020)
	Present 2-year results from PD-1102 trial (2H 2020)
	Initiate RESTORE-2 pivotal trial (2H 2020)
VY-HTT01 for Huntington's Disease	Provide update on program and clinical plans (mid-2020)
	Present additional results from preclinical studies (2H 2020)
Pipeline and Platform	Provide update on Friedreich's ataxia program
	Provide progress update on vectorized antibody efforts
	Present results from novel capsid efforts and new discovery programs