
Voyager®
THERAPEUTICS
Developing Life-Changing Therapies for
Devastating Neurological Diseases
January 2020

Forward-Looking Statements

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Building a Leading Neuro Gene Therapy Company

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

Lead program (VY-AADC in Parkinson's disease) in registration trial; **long-term follow-up data expected in 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

AAV Gene Therapy

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

Severe Neurological Diseases

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

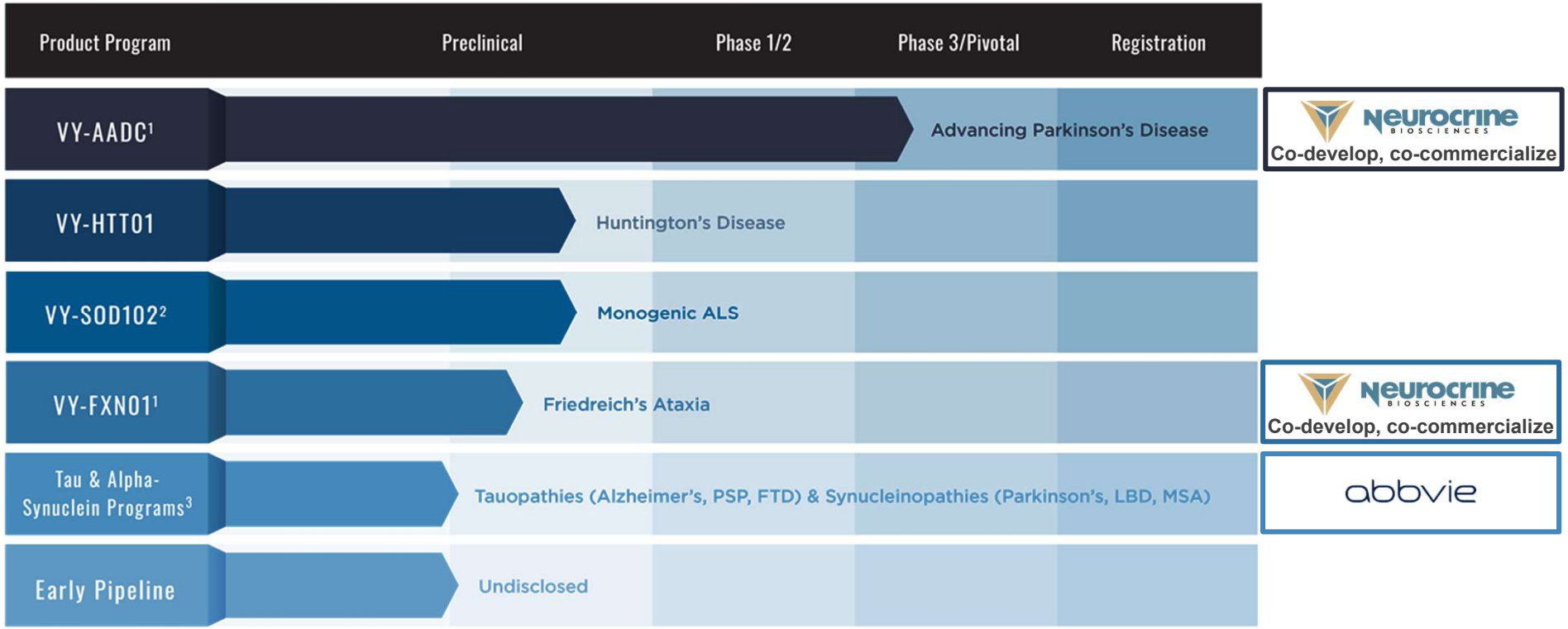
Vectorized Antibodies

Tauopathies (Alzheimer's, PSP, FTD)

Synucleinopathies (Parkinson's, LBD, MSA)

Undisclosed early pipeline programs across all modalities

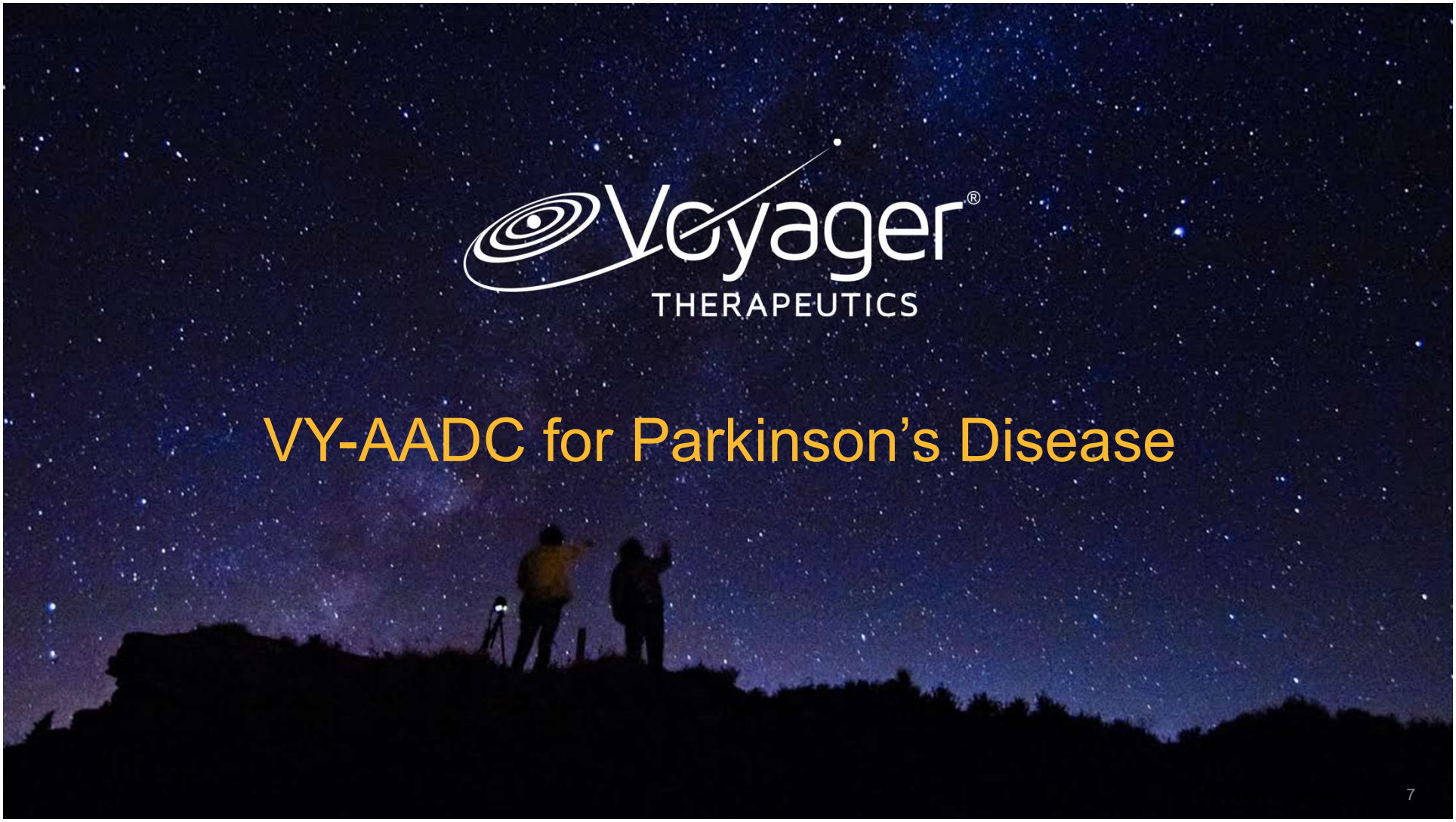
Focused on Severe Neurological Diseases



(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

Significant Progress Expected Across 2020

Program	Expected Milestone
VY-AADC for Parkinson's Disease	Present 3-year results from PD-1101 trial and 2-year results from PD-1102 trial
	Present initial results from PD-1104 extension study
	Continue enrollment of RESTORE-1 registration trial
	Initiate RESTORE-2 registration trial
VY-HTT01 for Huntington's Disease	Submit U.S. IND filing
	Initiate Phase 1 clinical trial
	Present additional results from preclinical studies
Pipeline	Select development candidate for Friedreich's ataxia program
	Provide progress update on vectorized antibody efforts
	Provide update on new programs and platform
	Present results from novel capsid efforts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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

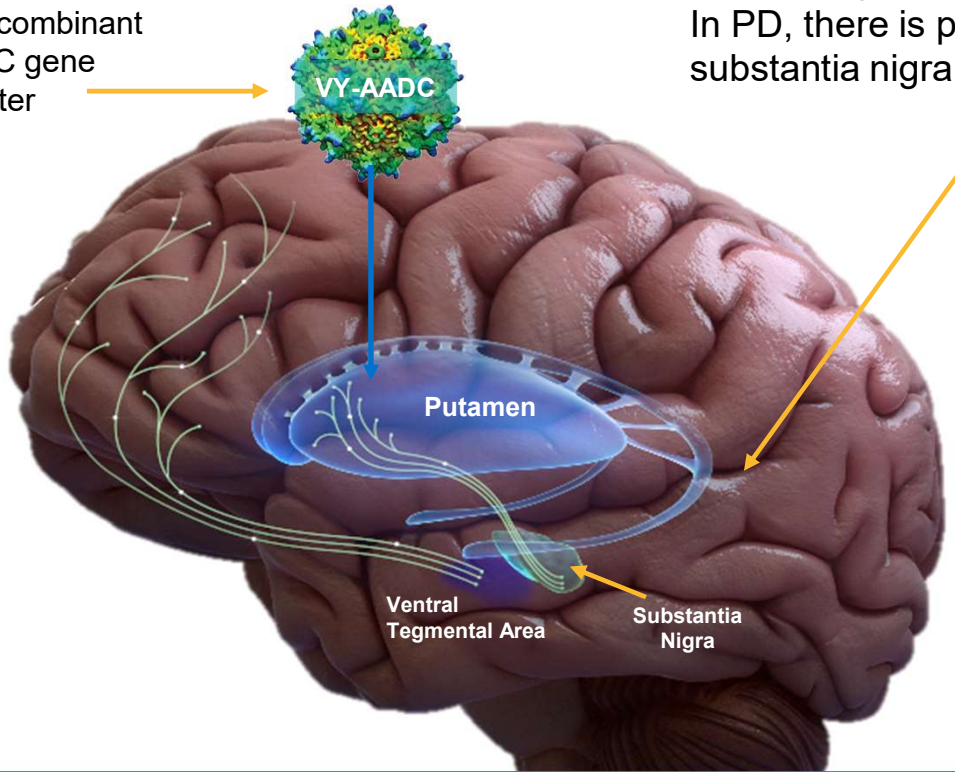
Voyager Clinical Development

- Currently enrolling VY-AADC Phase 2 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

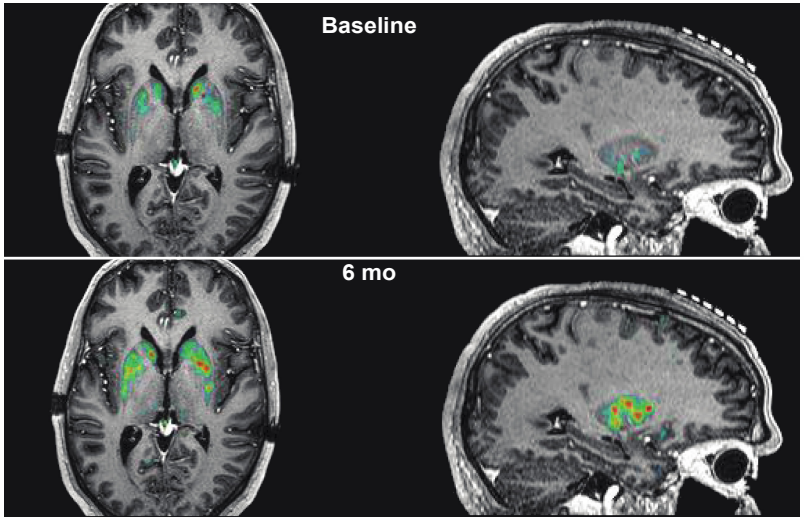


The Ability to Make AADC is Lost as PD Advances
In PD, there is progressive loss of fibers from the substantia nigra to the putamen

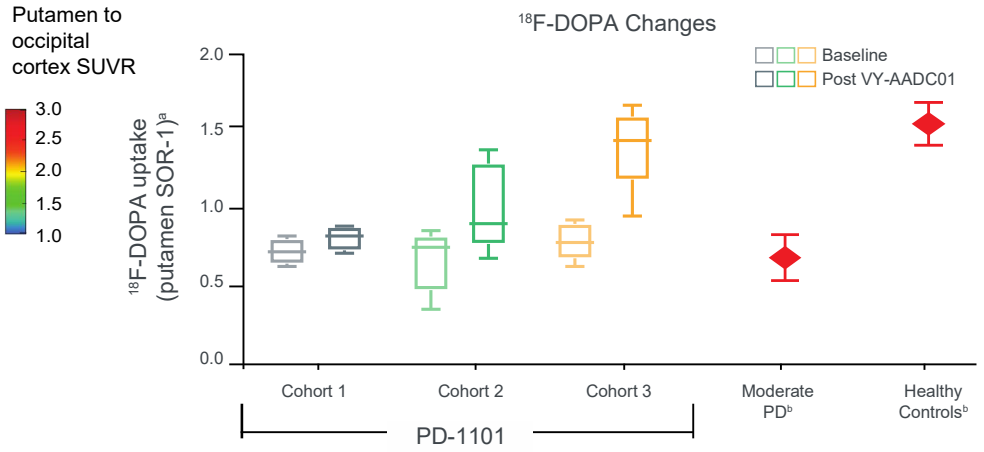
Approach: Introduce AADC to Healthy Postsynaptic Neurons in the Putamen
to replace degrading enzyme, improve levodopa sensitivity, and potentially improve clinical motor function

Demonstrated Improvements to AADC in Phase 1 Studies

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



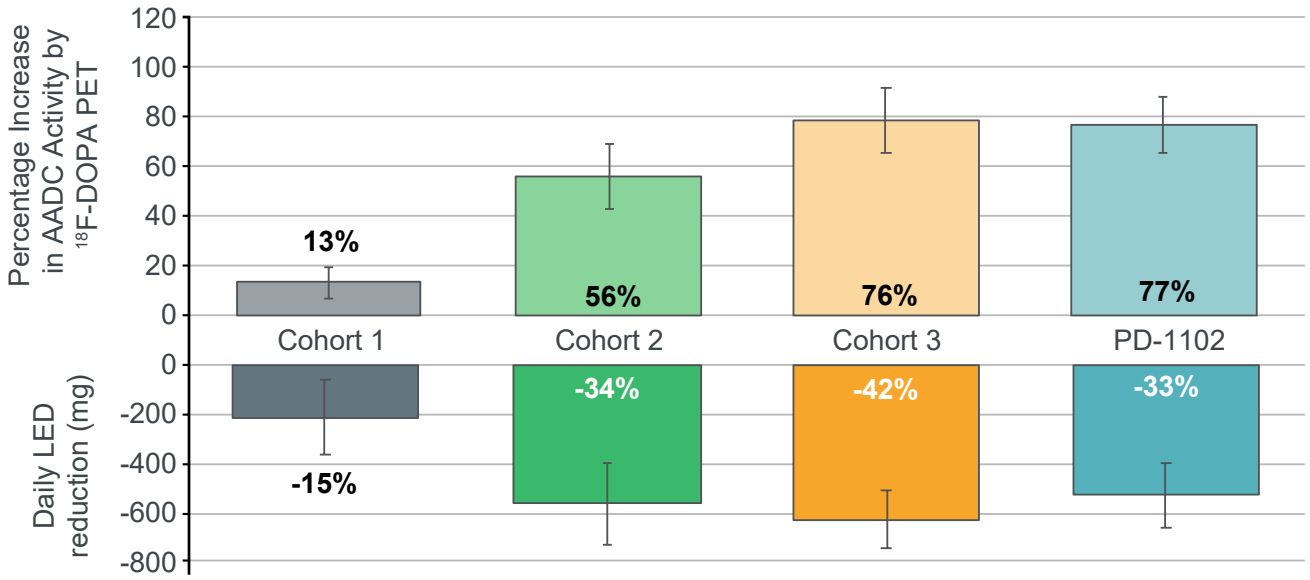
PET, Positron Emission Tomography



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:

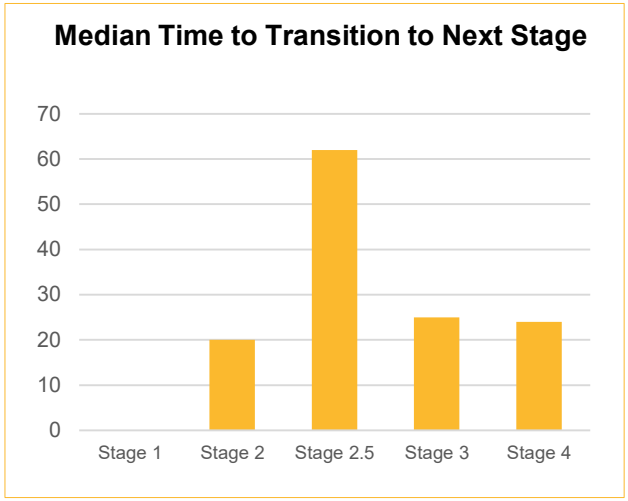
- 21% reduction for Cohort 2 at 2 years
- 43% reduction for Cohort 3 at 18-months

Source: Voyager Therapeutics

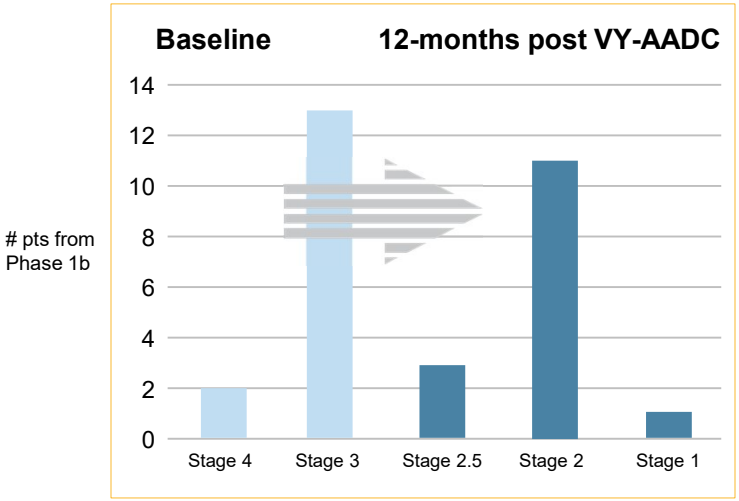
VY-AADC Phase 1: Shift in Disease Staging

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

Zhao et al.



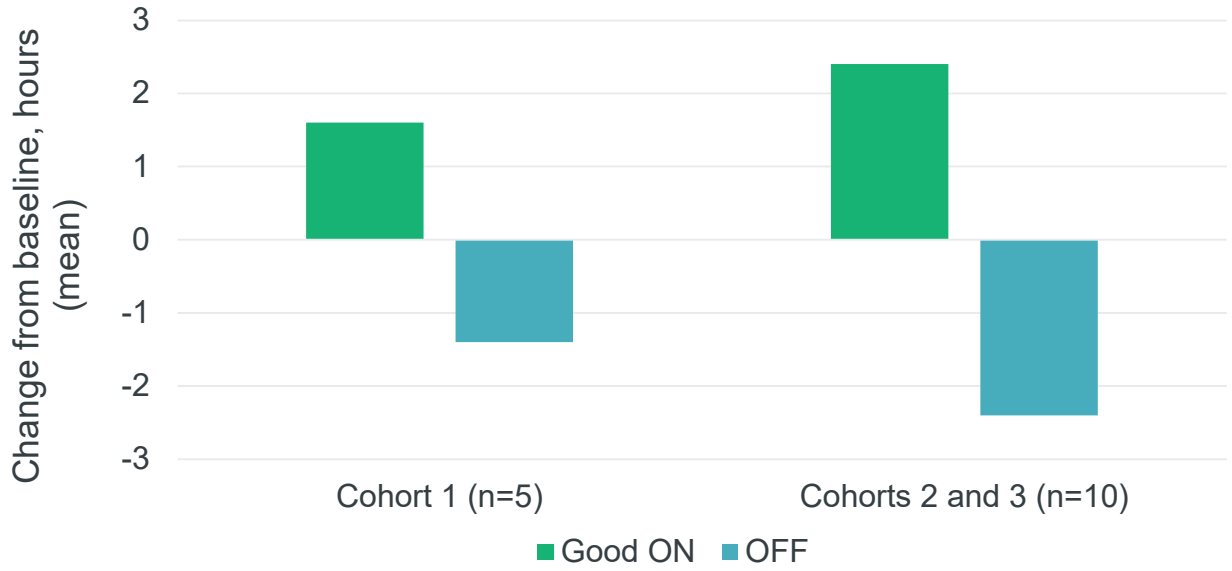
VY-AADC Phase 1b results



(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

Clinically Meaningful Improvements Demonstrated in Phase 1

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



Source: Voyager Therapeutics press release 11/7/18

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

RESTORE-1,-2: Registration Trials of VY-AADC

RESTORE-1 and -2: Randomized, double-blind, placebo-controlled trials 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

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 endpoint

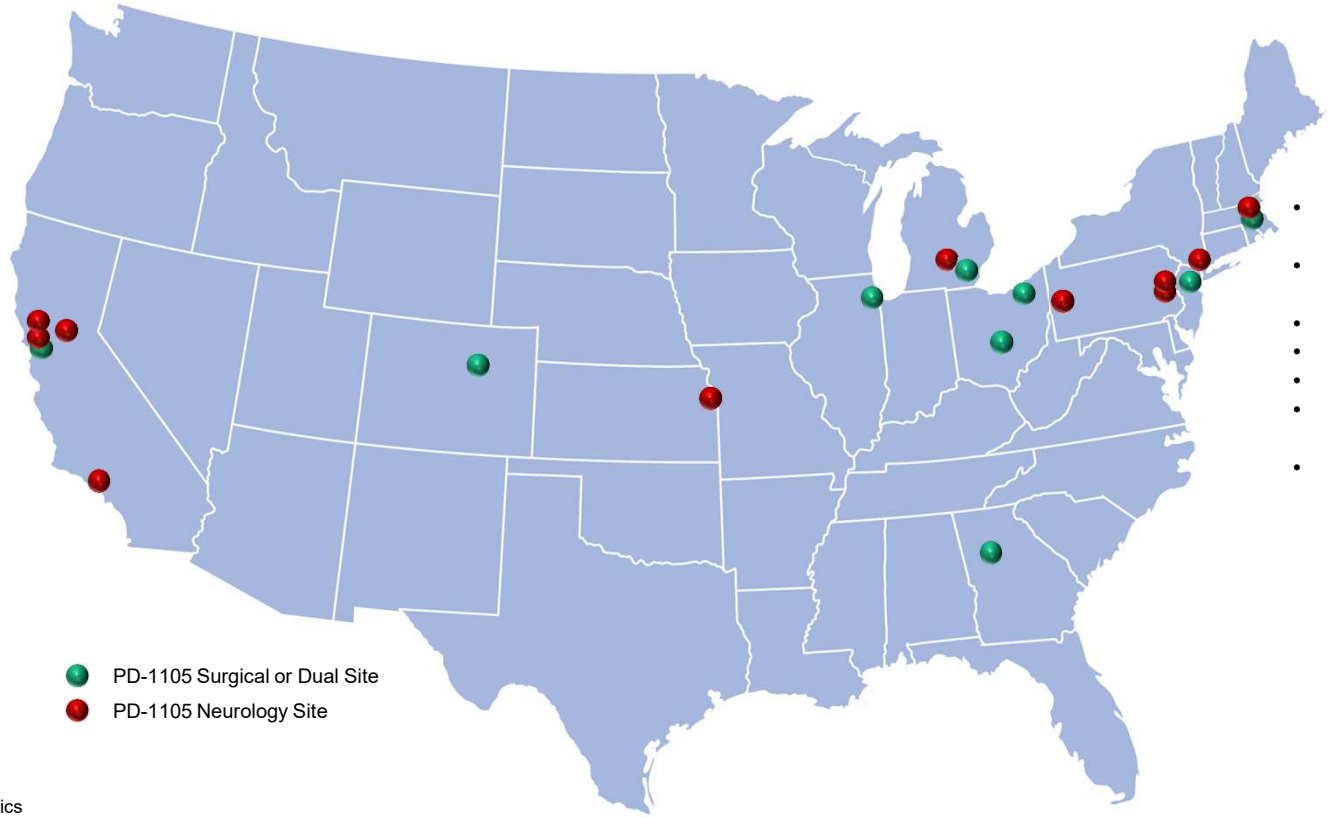
- Diary OFF time
- Changes in daily doses of oral levodopa
- Other motor function and quality of life measures from the UPDRS-II,-III scores, the PDQ-39, and PGI and CGI scores.
- The trial will also measure non-motor symptoms from NMSS

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
- 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.

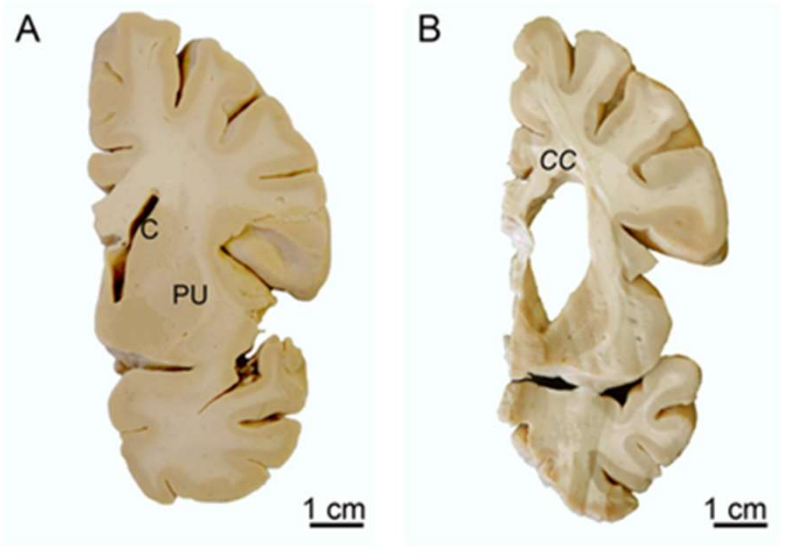
Overview

- 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

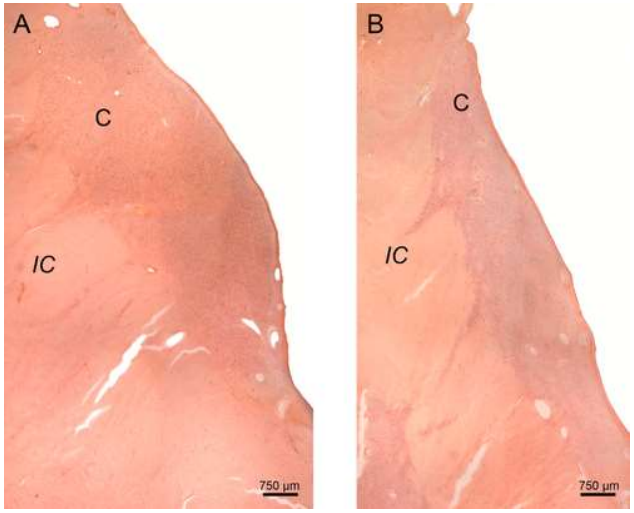
- VY-HTT01: anti-HTT RNAi gene therapy to knockdown HTT mRNA in striatum and cortex to slow disease progression
- VY-HTT01 in IND-enabling studies

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

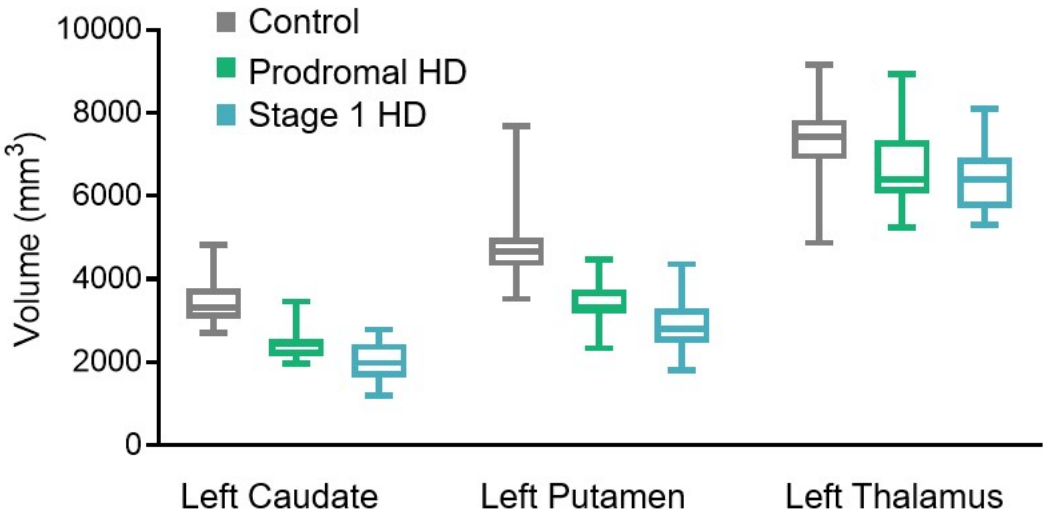


(A) Frontal section through the head of the caudate nucleus (C) of a representative control individual.

(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



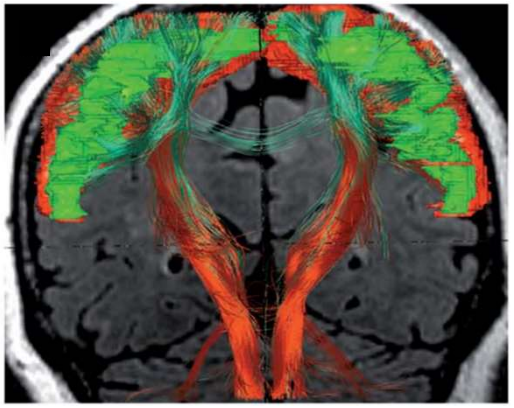
Wide range of structural sizes necessitates wide range of infusion volumes to achieve target coverage

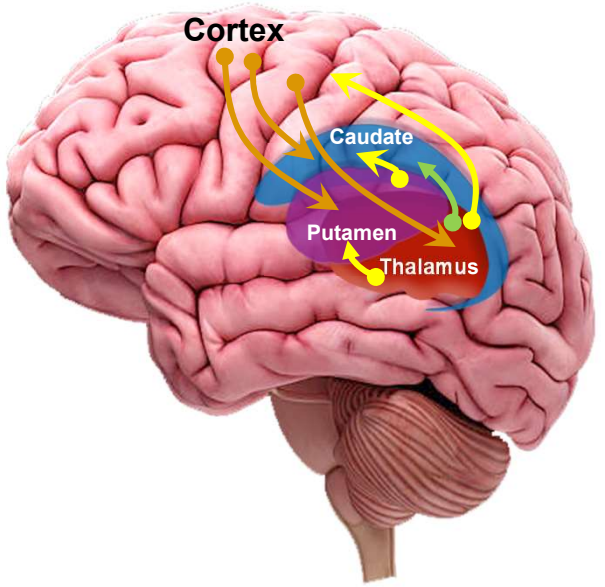
Voyager data on file from study in collaboration with Massachusetts General Hospital. Box and whisker plot shows medians (central lines) 25th and 75th percentiles (boxes), and minima and maxima (bars).

Putamen and Thalamus Route of Delivery Leverages Rich Connections

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



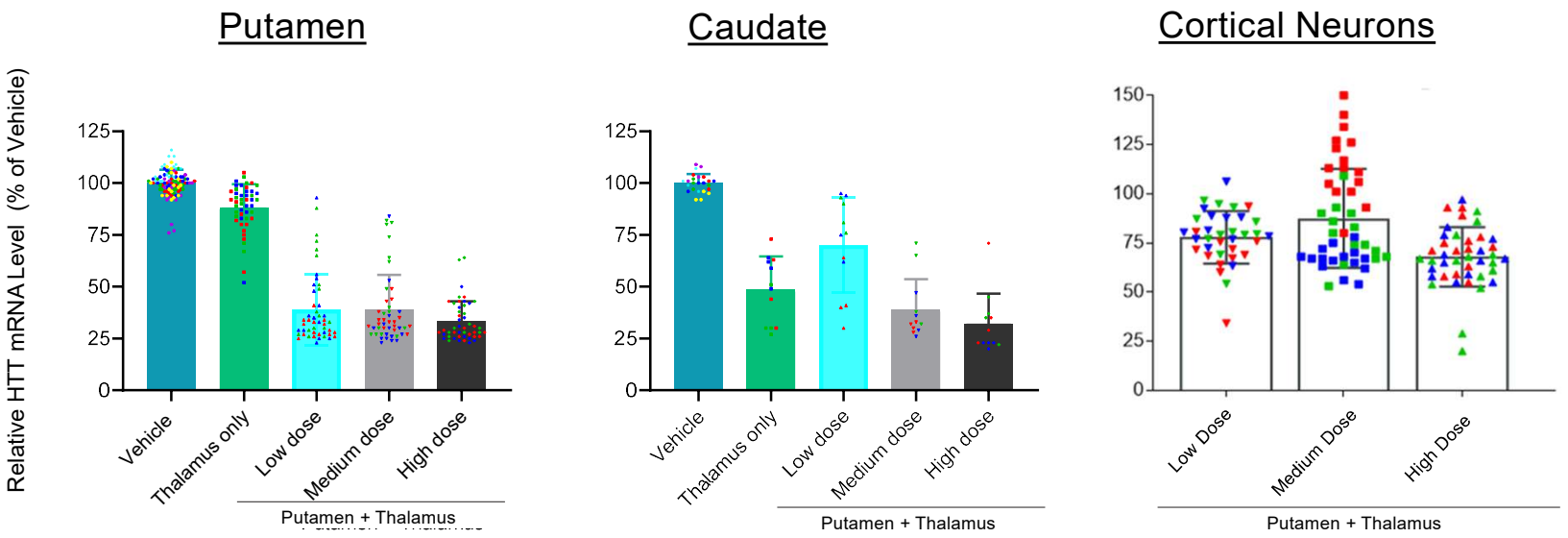


Laser capture microdissection of neurons from cortical regions showed that dose-dependent increases in vector genomes were detectable in 100% of neurons sampled in animal studies

Tractographical model of the cortico-basal ganglia and corticothalamic connections
Avecillas-Chasin, et al. 2016 Clin Anat 29:481-92

Robust HTT mRNA Lowering in Adult NHPs at 5 Weeks

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



Source: ESGCT 2018 Poster P190
(1) Putamen and Caudate lowering measured from tissue punches; Cortical neuron lowering measured from laser-captured cortical neurons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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.)

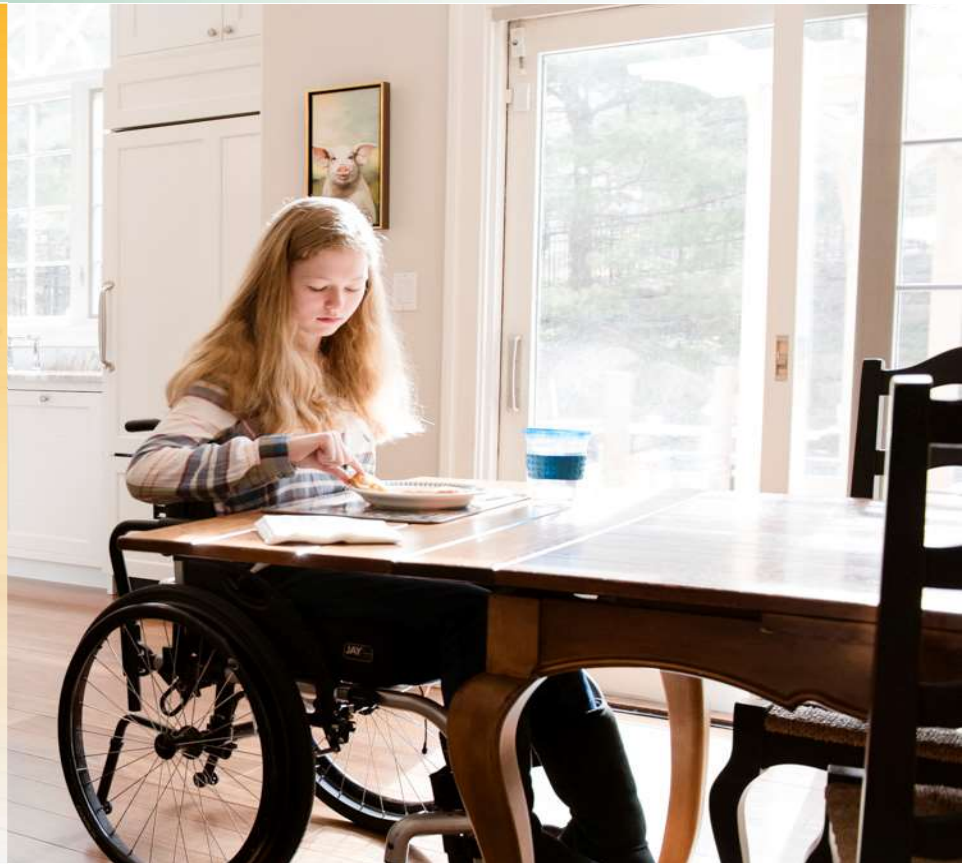
Friedreich's Ataxia: ~6,400 Patients in the U.S.

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

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	Provide update on new programs and platform
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