CAP-003: A Novel Investigational CNS-targeted Intravenous Gene Therapy for the Treatment of PD-GBA

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GBA1 Meeting
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Disclosures

- Kimberly McDowell, Ph.D., is an employee of Capsida Biotherapeutics

Solving the Challenges of Gen-1 Genetic Medicines

Starting in CNS and Ophthalmology with IP rights and applicability across all therapeutic areas

	CNS Challenges	Capsida Solutions
Crossing the BBB	Limited ability to cross BBB; < 1% neuronal transduction	>70% of neurons transduced in NHPs
Safety Concerns	Liver and dorsal root ganglia (DRG) toxicity	>16x liver & >50x DRG detargeting; lower dosing
Patient Populations	Narrow therapeutic index (TI) limits to ultra-rare/rare diseases	Broader TI = more common diseases across ages
Route of Administration	Direct injection to brain or CSF causes significant risks and inconsistent expression	IV delivery avoids risks of invasive delivery and allows for consistent expression
	IV delivery increases risk of off-target effects (esp. liver) and triggering immune response	Well-tolerated safety profile with no adverse histopathological findings

Near Clinical Stage Wholly-owned Programs

First human POC by end of 2025

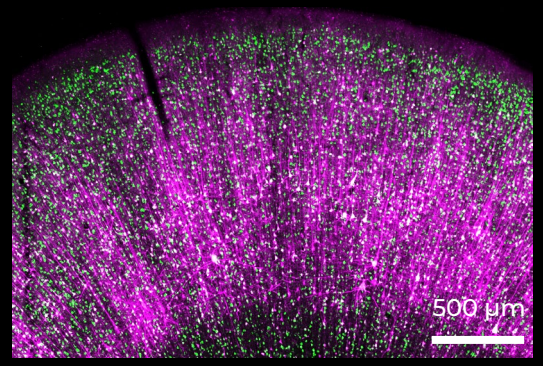
Disease / Target	Preclinical	IND-Enabling	Phase 1/2	Key Catalysts
STXBP1 Developmental and Epileptic Encephalopathy (STXBP1-DEE)	First-in-class CAP-002			2024 Q4 ✓ ODD received 2025 Q2 ✓ IND clearance received Q2 ✓ Fast-track designation received Q3 - First patient dosed 2026 Q1 - First efficacy data
Parkinson's disease associated with GBA mutations (PD-GBA)	Best-in-class CAP-003			2025 Q2 - IND filing Q3 - First patient dosed Q4 - First biomarker data 2026 Q3 - First efficacy data (1 yr)
Friedreich's ataxia (FA)	Best-in-class CAP-004			2025 Q1 - IND-enabling studies ongoing Q3 - Traditional & self-regulating cargo results 2026 Q2/Q3 - IND filing

Capsida is the first genetic medicines company with FDA IND clearance for an engineered IV-delivered gene therapy that crosses the blood-brain-barrier and detargets liver

Lead Capsid Transduces Majority of Neurons Throughout the CNS Across 3 Wholly-Owned Programs at Low E13 vg/kg Dose

Cortex: Genetic Epilepsy

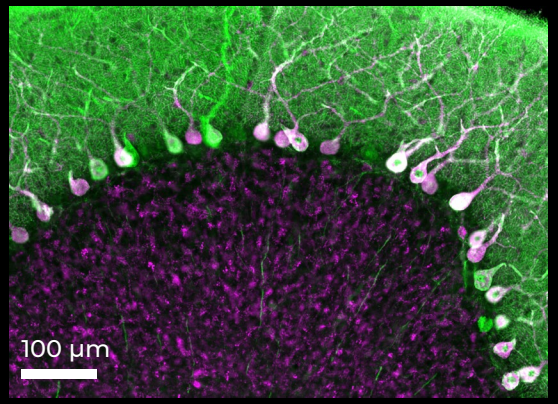
Frontal Cortex



HA-GOI NeuN

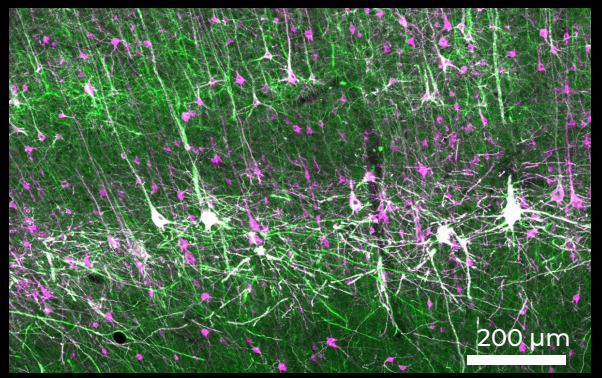
Motor neurons and deep cerebellar nuclei: Friedreich's Ataxia

Cerebellum



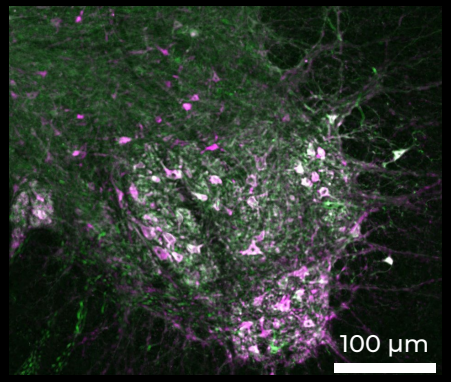
HA-GOI CALBINDIN

Motor Cortex



HA-GOI SMI32

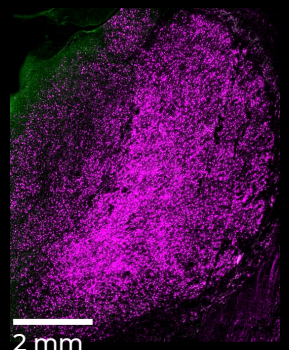
Spinal Cord



HA-GOI SMI32

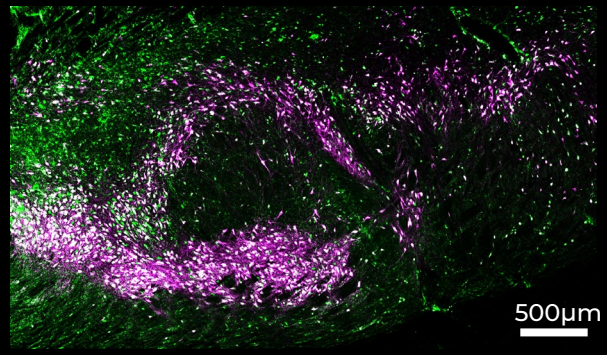
Deep brain structures: Parkinson's Disease

Thalamus

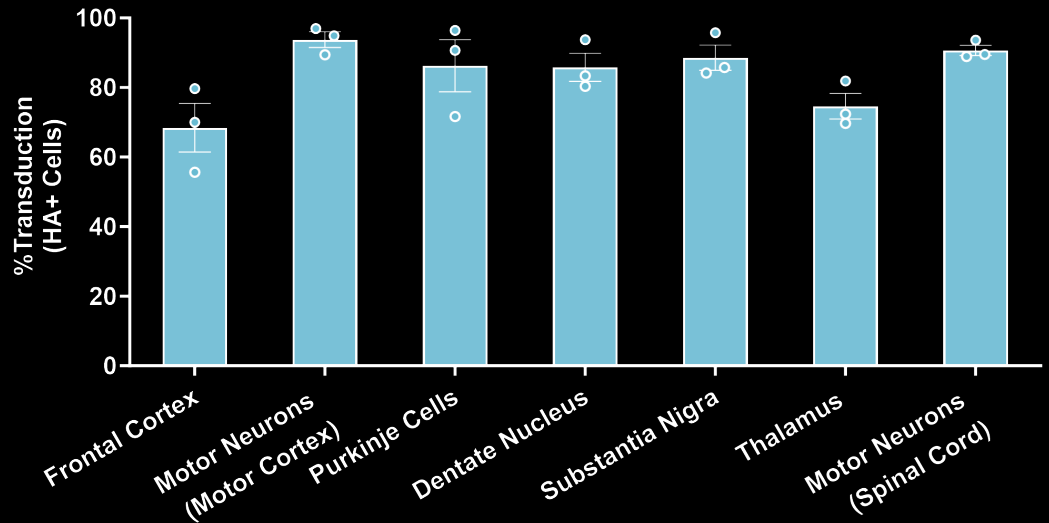


HA-GOI NeuN

Substantia Nigra

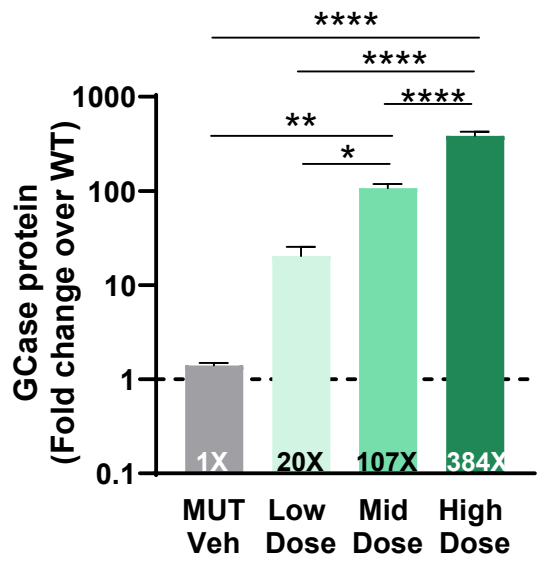


HA-GOI TH

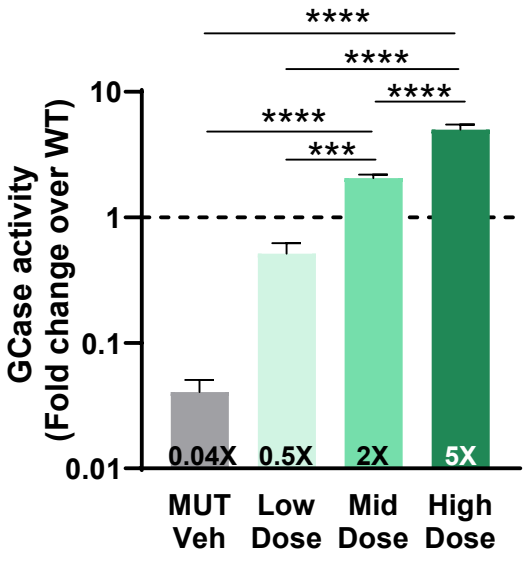


Mouse model correction supports disease-modifying potential of *hGBA1* clinical cargo

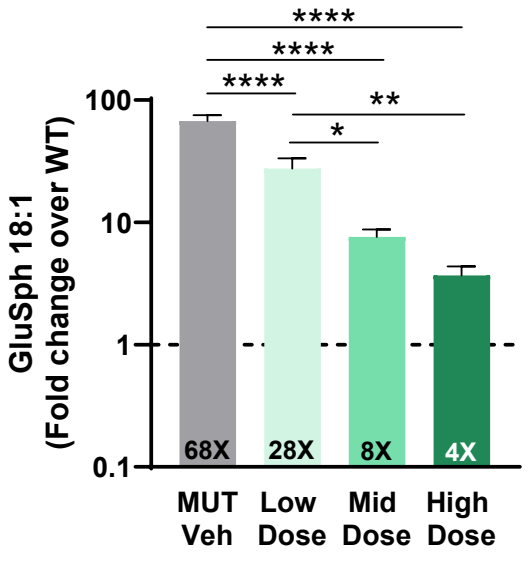
GCase Protein



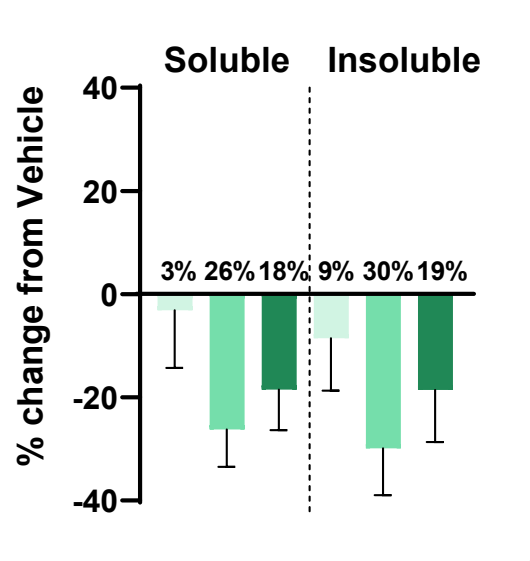
GCase Activity



GluSph



α - Synuclein

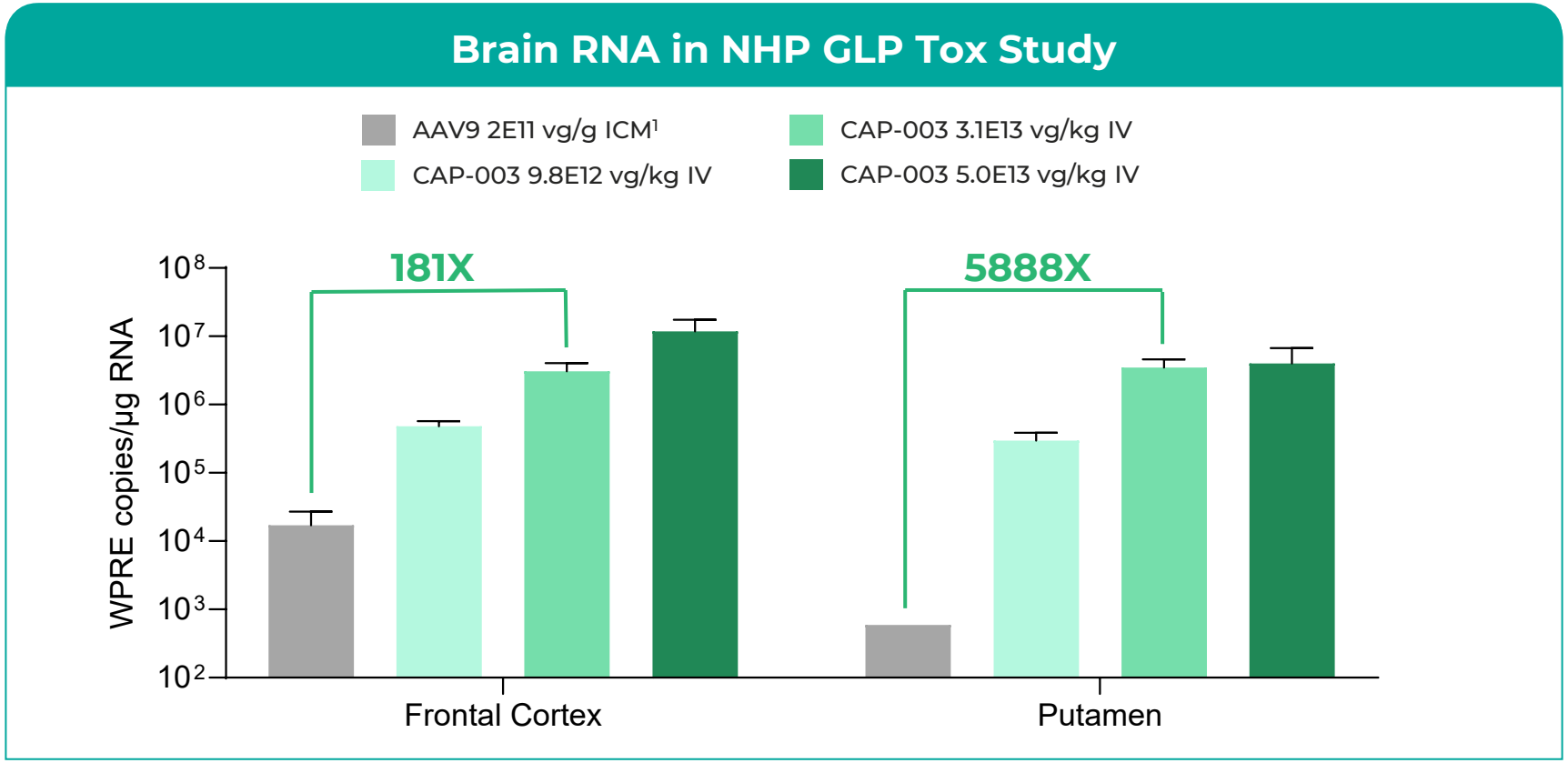


- The disease model exhibits a more severe phenotype (>90% GCase activity reduction, ~6800% GluSph increase) compared to PD-GBA patients (~30% GCase activity reduction[1], ~40% GluSph increase[2])
- Delivery of *hGBA1* via surrogate capsid results in dose-dependent increases in GCase protein and activity in the brain
- Increased activity coincides with significant decreases in GluSph levels, and reductions in α-synuclein

Pharmacology Study
In-life: 6 months
Species: Mus musculus (n=10/grp)

[1] Leyns et al., 2023; [2] Munoz et al., 2021

IV-delivered CAP-003 Achieves Superior RNA Expression Compared to ICM-delivered AAV9 in NHPs

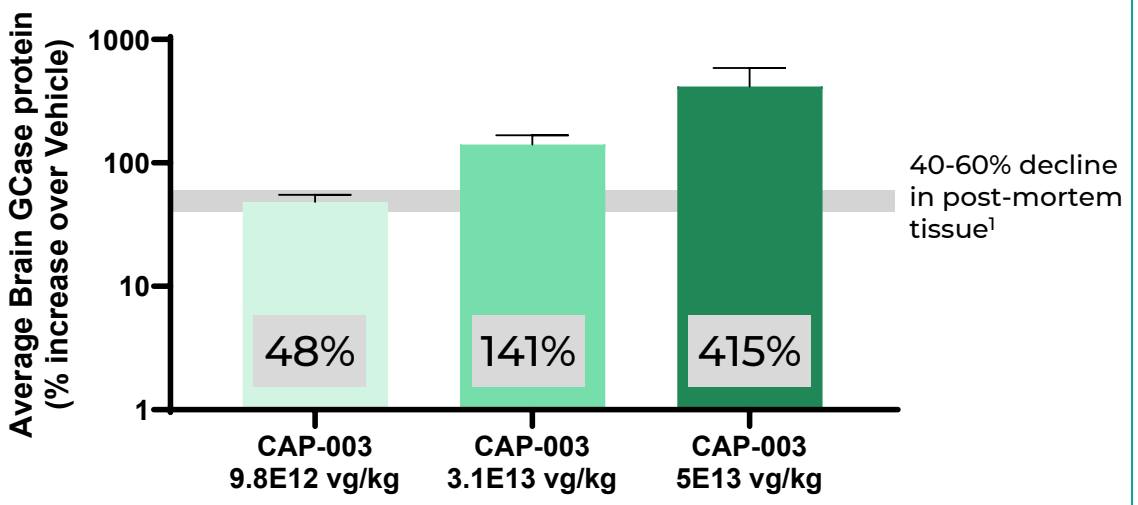


[1] AAV9 ICM data generated from past Capsida study with same expression cassette (promoter, regulatory elements, etc.) but different therapeutic cargo; no protein or %neuron comparison possible

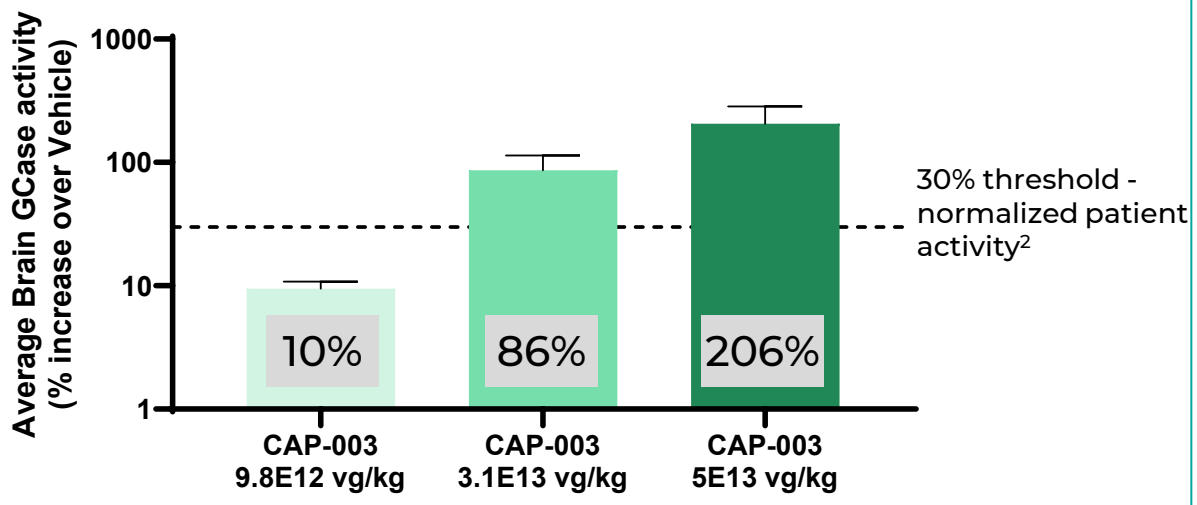
GLP Tox Study
In-life: 3 months
Species: Cynomolgus macaques (n=3/grp)

CAP-003 maintains significant increased brain GCase protein and activity at 3 months post-dosing in NHP GLP Tox study

Brain GCase Protein



Brain GCase Activity



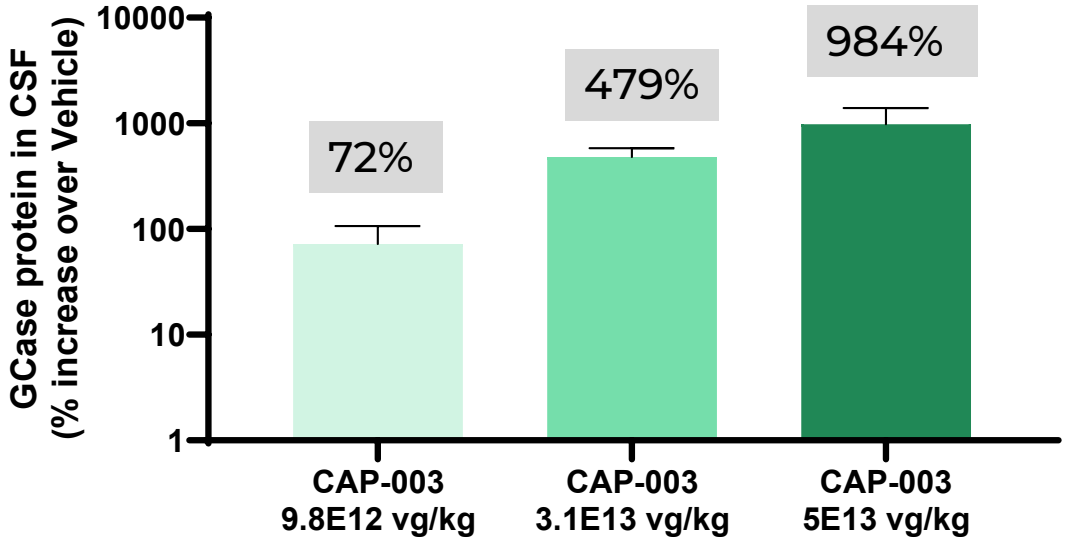
- Administration of CAP-003 resulted in a dose-dependent increases in average brain GCase protein and activity when normalized to the vehicle control (i.e., endogenous GCase levels)
- Expression of GCase over endogenous levels was well-tolerated in Capsida-conducted studies and supported by other published literature using neuronal cultures, mouse, and NHP studies (Sucunza 2021, Okai 2024)
- CAP-003-mediated increases in GCase activity has the potential to provide clinically meaningful benefits to PD-GBA patients

GLP Tox Study
In-life: 3 months
Species: Cynomolgus macaques (n=3/grp)

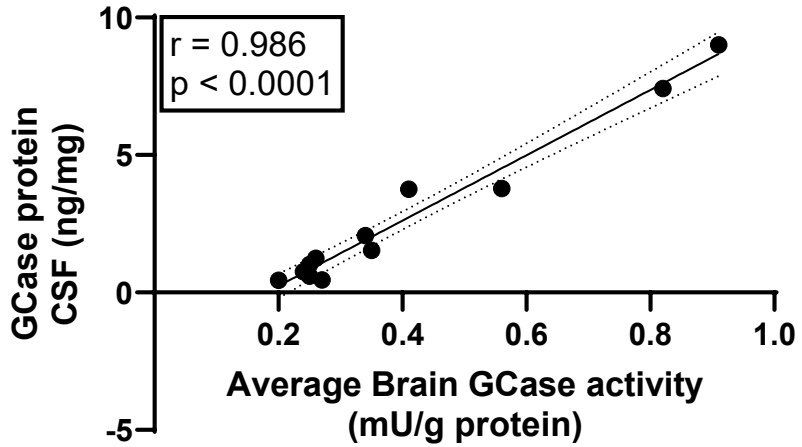
[1] Munoz et al., 2021; [2] Leyns et al., 2023

GCase protein level in CSF serves as potential pharmacodynamic biomarker for brain GCase activity

CSF GCase Protein in NHPs



Correlation of CSF GCase Protein & Brain GCase Activity in NHPs

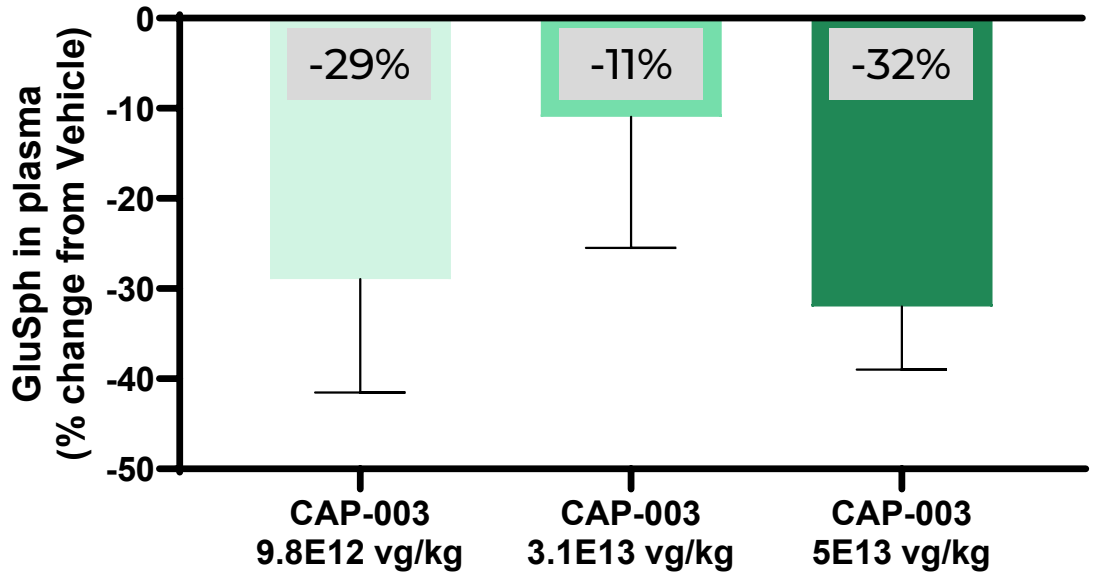


- Administration of CAP-003 resulted in a dose-dependent increase in GCase protein levels in the CSF when normalized to the vehicle control
- Significant positive correlation between CSF GCase protein levels and brain GCase activity

GLP Tox Study
In-life: 3 months
Species: Cynomolgus macaques (n=3/grp)

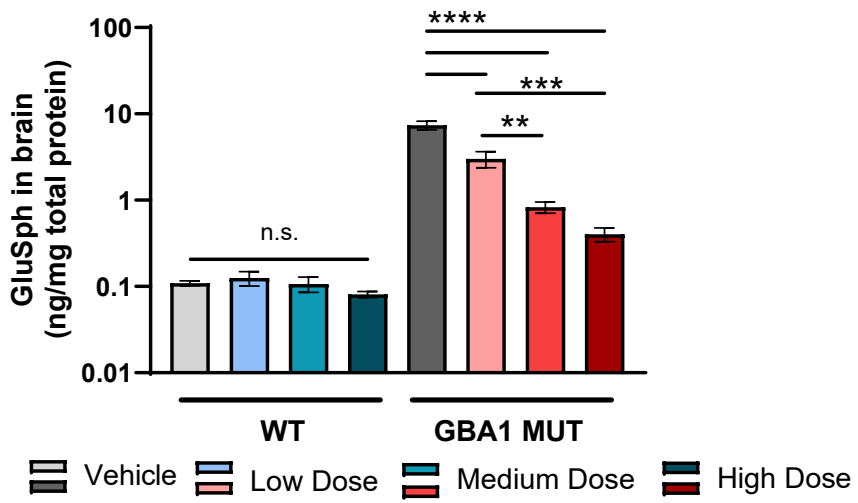
Decreased plasma GluSph levels supports target engagement in healthy NHPs

Primates - Plasma GluSph



GLP Tox Study
In-life: 3 months
Species: Cynomolgus macaques (n=6/grp)

Mice - Brain GluSph

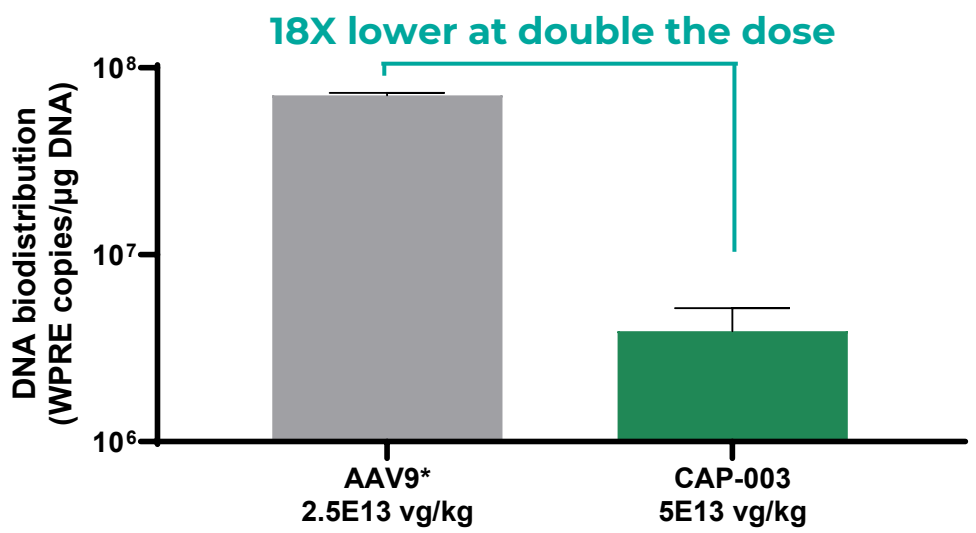


Pharmacology Study
In-life: 6 months
Species: Mus musculus (n=10/grp)

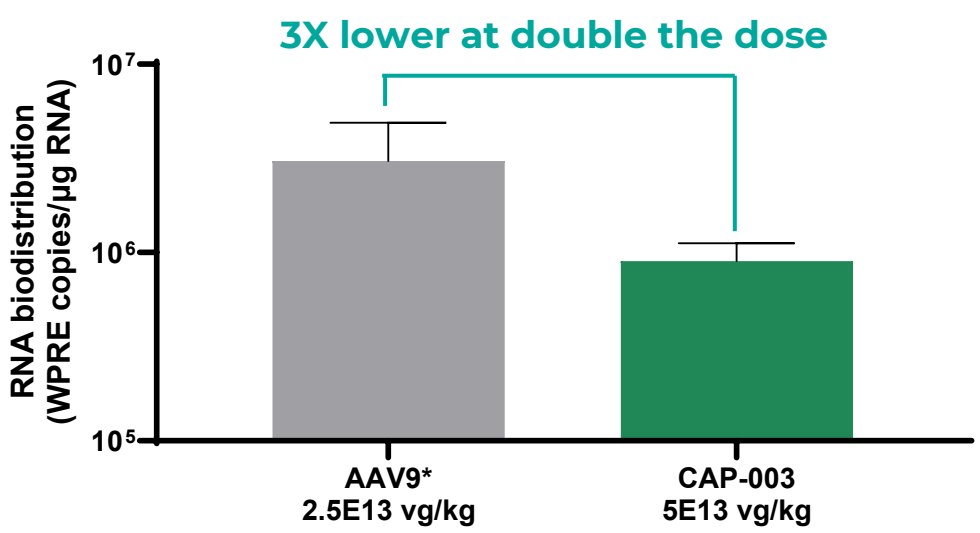
- In healthy NHPs, GluSph levels are already low in the plasma and undetectable in the CSF; CAP-003 administration shows target engagement via modest decreases in GluSph levels when normalized to the vehicle control
- Similar modest decreases from baseline are seen across WT NHPs and mice, whereas elevated GluSph levels are significantly decreased in disease model mice after treatment

CAP-003 is Substantially Detargeted from Liver and DRGs in NHPs Compared to AAV9

Liver DNA



DRG RNA



- Despite being delivered at higher doses, CAP-003 remains detargeted compared to AAV9 in liver and DRGs
- CAP-003 is safe and well-tolerated in the GLP Toxicology study, with no adverse clinical pathology or histopathological findings throughout the CNS, DRGs, and peripheral organs (including liver) up to NOAEL of 5E13 vg/kg

*Historical IV-delivered AAV9 2.5E13 vg/kg (non-GBA cargo control)

GLP Tox Study
In-life: 3 months
Species: Cynomolgus macaques (n=3/grp)

CAP-003 (PD-GBA) Phase 1/2 Clinical Plan

Clinical Ph1/2 Planning

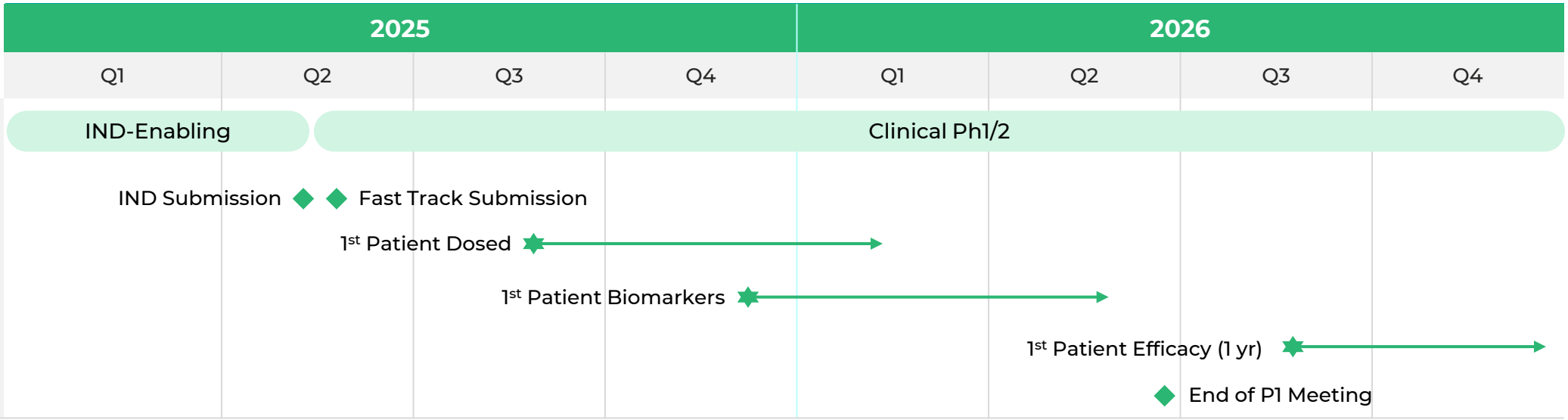
Population

- Ages 21-75 years
- PD Hoehn & Yahr Stage 1-3
- Ph1: 6 patients

Key Measurements

- Safety
- Biomarkers (e.g., GCase, GluSph, & GluCer)
- 1 & 2-year efficacy (e.g., MDS-UPDRS, cognition, etc.)

CAP-003 (PD-GBA) Program Overview



GluSph = glucosylsphingosine; GluCer = glucosylceramide;

MDS-UPDRS = Unified Parkinson's Disease Rating Scale

CAP-003 potential as best-in-class gene therapy for PD-GBA

- Capsida's PD-GBA candidate efficiently crosses the blood-brain barrier in NHPs after intravenous injection and achieves breakthrough levels of transduction throughout the brain while significantly de-targeting the liver (>15-fold) compared to AAV9
- We have characterized a human receptor that binds our engineered capsids; this receptor has complete homology between humans and macaques in the predicted binding pocket
- Significant phenotypic correction in a *GBA1* loss-of-function mouse model supports disease-modifying potential of *hGBA1* clinical cargo
- GCase enzyme activity is raised significantly (>200% over endogenous levels) in therapeutically relevant areas of the NHP brain, exceeding levels needed to restore GCase function in patients with PD-GBA
- In the GLP Toxicology study, this efficacy was achieved at low to moderate doses that are well tolerated in NHPs without remarkable changes in clinical pathology or immunogenicity, with no adverse histopathology findings across the body, including liver and DRGs
- CAP-003 scales well in suspension manufacturing platform to meet quantity and quality for the clinic
- Capsida's PD-GBA program is currently on track for IND clearance in Q2 2025 and FIH in Q3 2025

CAPSIDA BIOTHERAPEUTICS

Our Pipeline is Making the Impossible Possible

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