CAP-003, a CNS-Targeted IV-delivered AAV Gene Therapy, Safely Increases Brain GCase in NHPs to Level Supporting Potential Normalization of Activity in PD-GBA Patients

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Introduction

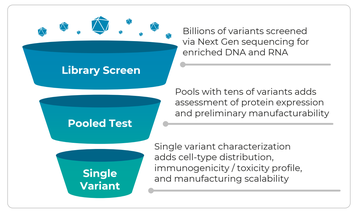
The GBA1 gene encodes a lysosomal hydrolase enzyme, glucocerebrosidase (GCase), which metabolizes glycolipids within the lysosomal compartment. Mutations in this gene result in decreased GCase activity, leading to accumulation of glycosphingolipids that are thought to contribute either directly or indirectly to α-synuclein pathology, the pathological hallmark of PD[1]. Substantial preclinical evidence suggests that interventions targeted to restore GCase activity in the brain could slow or stop the progression of PD-GBA[1,2].

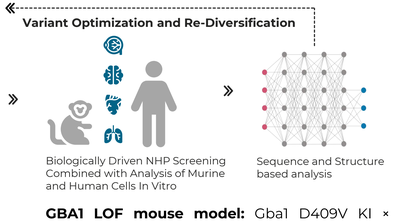
Capsida is developing a gene supplementation therapy candidate (CAP-003) to be administered as a single intravenous (IV) infusion to PD-GBA patients. CAP-003 consists of an engineered AAV capsid that is designed to deliver the functional human *GBA1* gene broadly across the CNS while de-targeting the liver and DRGs to improve the safety profile. This novel capsid has recently enabled IND approval for another Capsida owned program (CAP-002). Using a loss-of-function mouse model, we provide proof-of-concept pharmacology demonstrating that administration of the therapeutic cargo using a surrogate capsid results in dose-dependent increases in GCase activity that coincide with dose-dependent decreases in glucosylsphingosine as well as reductions in α-synuclein levels.

In a non-human primate GLP toxicology study, administration of CAP-003 at clinically relevant doses results in robust expression across key brain regions, with increases in levels of GCase protein and activity that show strong correlations with similar measurements in biofluids. No adverse clinical pathology, immunogenicity, or histopathological findings were observed at any of the doses. Given that a ~30% decrease in brain GCase activity is expected in the patient population[3], the observed increases may normalize activity levels, reduce glycolipids, and potentially slow or stop the progression of PD-GBA.

Methods and Materials

NHP-Driven Capsid Engineering Platform





NHP GLP Toxicology: CAP-003 was administered IV to juvenile WT male and female cynomolgus macaques at 3 doses. After 3-months, DNA and RNA biodistribution were assessed using ddPCR. GCase protein, GCase activity, and glucosylsphingosine levels were measured via mass spectrometry in brain tissue, plasma, and CSF to allow for early assessment of planned clinical target engagement biomarkers.

GBA1 LOF mouse model: Gba1 D409V KI × mThy1-hSNCA and WT mice received a retroorbital IV injection at 8-weeks of age. After 6-months cargo DNA and RNA were assessed using ddPCR. GCase protein, activity, and glycosphingolipid content were assessed in CNS tissue using mass spectrometry and α-synuclein was assessed via ELISA. A surrogate capsid (CAP.B10) was used to deliver the therapeutic cargo enabling assessment of target engagement in CNS tissue achieved by a capsid that crosses the BBB in mice.

Figure 1. NHP-Driven Capsid Engineering Platform utilized to identify Capsid for CAP-003 for PD-GBA

Capsida's high-throughput screening process in NHPs identifies capsids that target desired tissues and cell types while de-targeting undesired tissues such as liver and dorsal root ganglia which have been associated with adverse events with other gene therapies

Results

In vivo target engagement in a GBA1 LOF mouse model following administration of CAP.B10-hGBA1 shows robust target engagement and significant reductions in key substrates

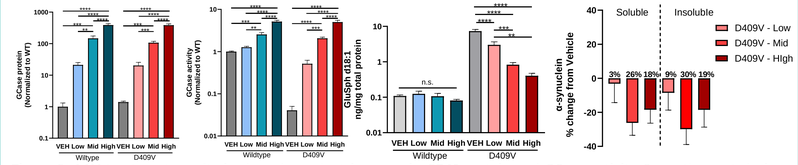
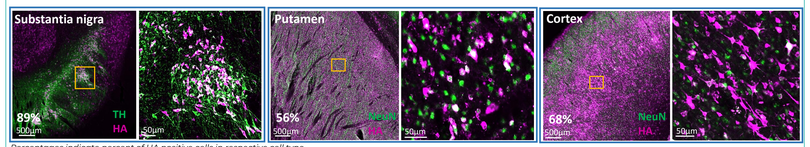


Figure 2. AAV treatment results in dose-dependent increase in GBA1 protein and GCase activity 6-months post dosing. These increases coincide with decreases GluSph and α-synuclein levels in the brain and demonstrate robust target engagement of the CAP-003 hGBA1 cargo. GluSph 18:1 = Glucosylsphingosine. ****p<0.0001, ***p<0.001, **p<0.01.

IV administration of CAP-003 in NHP GLP Toxicology study shows superior brain wide expression and is de-targeted from the liver and dorsal root ganglia relative to WT AAV9



Percentages indicate percent of HA positive cells in respective cell type

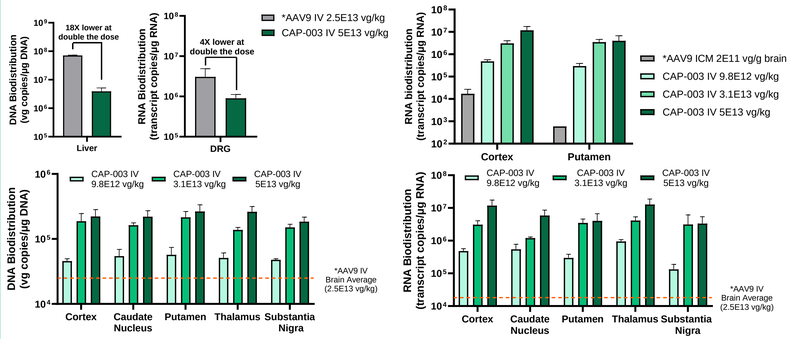


Figure 3. Representative histology (and neuronal transduction percentage) in key brain regions after IV administration of CAP-003 capsid packaging epitope tagged cargo. IV administration of CAP-003 in primates in a GLP Toxicology study results in robust DNA biodistribution and mRNA expression across key areas of interest in the CNS while de-targeting peripheral organs including the liver and DRGs reducing safety risks associated with WT AAV9. *Data from historical WT AAV9 studies

Results

Increases in GCase protein and activity in the NHP brain significantly surpass expected therapeutic threshold and correlate with key biomarkers at 3-months post-dose in GLP Toxicology study

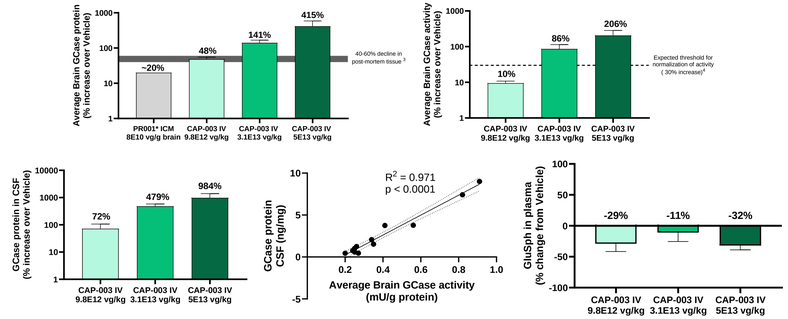


Figure 4. Administration of CAP-003 in primates results in >400% increases in GCase protein and >200% increases in GCase activity in the brain, exceeding levels that are expected to be clinically meaningful. Measurements of key fluid biomarkers show strong relationship to GCase activity in the brain across doses tested. *Reported by Prevail (Source: 2019 S1 filing) in their nonclinical NHP study (~20% increase across cortex, hippocampus, midbrain)

	Limitations of Investigational Therapies	CAP-003 Differentiators
Neuronal Transduction	Low neuronal transduction, especially in deep brain structures like the substantia nigra	>70% of neurons transduced in cortical and subcortical brain regions
GCase Elevation	Limited GCase elevation	GCase increases > levels needed to treat PD-GBA; reaching >200% on average across key brain regions
Delivery	Direct injection to the brain or CSF is invasive and results in inconsistent expression	IV delivery limits risks and allows for broad coverage across the CNS
Safety	Liver and DRG toxicity risks	No adverse histopathology findings in surveyed NHP organs, including liver and DRGs

Conclusions

- Proof-of-concept pharmacology in a GBA1 LOF mouse demonstrates dose-dependent increases in GCase protein levels and activity following administration of the CAP-003 hGBA1 cargo at 6-months post dosing. These increases coincide with decreases in key substrates that contribute to pathology in the PD-GBA patient population.
- In a GLP toxicology study, CAP-003 achieved broad CNS distribution in non-human primates, including high expression in regions impacted by PD-GBA pathology and increases in GCase activity expected to normalize levels in the PD-GBA patient population. Importantly, no adverse clinical pathology, immunogenicity, or histopathology was observed across any of the doses. Exploratory biomarkers show strong relationships to GCase activity in the brain which will be evaluated in clinical trials.
- CAP-003 is on track for IND clearance in 2Q 2025 and FIH in Q3 2025

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Presented on WEDNESDAY
- Systemic AAV Gene Therapy with Next Generation Engineered Capsid Demonstrates Expression Levels Supporting Potential Therapeutic Benefit for CNS, Cardiac, and Sensory Symptoms in Friedreich's Ataxia, 1:45-2:00 PM CT, Abstract Number: 75, Presenter: Celeste Stephany, Ph.D., Director of CNS and Ophthalmology Preclinical Research, Capsida
- Identification of Multiple Novel Blood-Brain-Barrier Receptors for CNS Gene Therapy and Other Drug Modalities via an Integrated AAV Capsid Engineering Platform, 2:45 – 3:00 PM CT, Abstract Number: 93, Presenter: Nick Goeden, Ph.D., Founder, Chief Technology Officer, Capsida
- Systemic Gene Therapy CAP-002 Demonstrates Potential for Disease-Modifying Treatment of Seizures and Motor and Cognitive Deficits of STXBP1-DEE Using an Engineered, CNS-Targeted AAV, 3:45-4:00 PM CT, Abstract Number: 123, Presenter: Nick Flytzanis, Ph.D., Founder, Chief Research and Innovation Officer, Capsida
- Dual-Platform NGS for Comprehensive Characterization of Engineered rAAV Vector Integrity,5:30 – 7:00 PM CT, Abstract Number: 1326, Presenter: Zach Mason, Associate Scientist, Capsida

Presented on TUESDAY
- rAAV Manufacturing Solutions: Strategic Designs of Engineered rAAV Two Plasmid Systems for Cost Effective Scaling and Product Safety, 5:30 – 7:00 PM CT, Abstract Number: 962, Presenter: Jenna Rodden, Senior Research Associate, Capsida

Presented on THURSDAY
- Development of a Novel Automated Loading Approach Which Significantly Reduces Processing Time for Enriching Full AAV Capsids Using Ultracentrifugation, 5:30 – 7:00 PM CT, Abstract Number: 1833, Presenter: Varun Gejji, Ph.D., Senior Scientist, Capsida

References

[1]Smith 2022
[2]Behl 2021
[3]Munoz 2021
[4]Leyns 2023