IND-Enabling GLP NHP Study of VY1706, a BBB-Crossing AAV Gene Therapy Targeting Tau in Alzheimer's Disease

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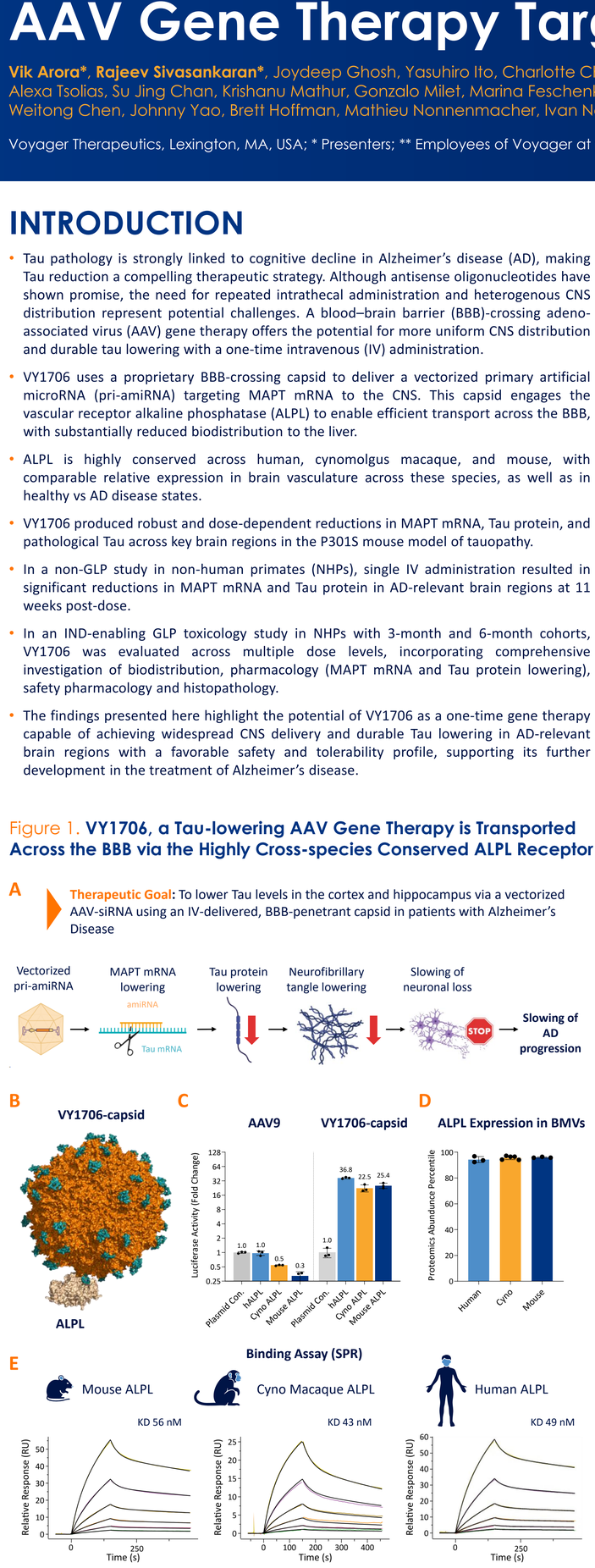
INTRODUCTION

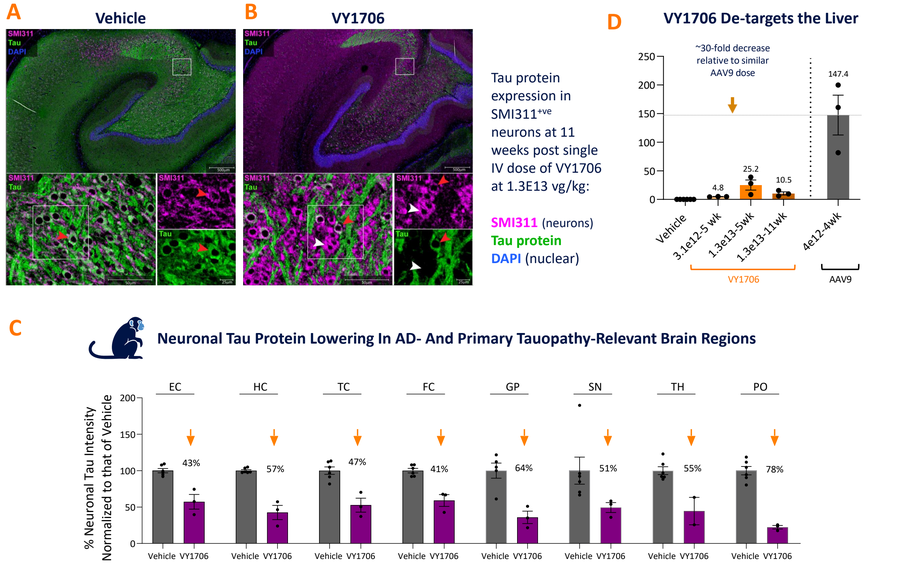
- Tau pathology is strongly linked to cognitive decline in Alzheimer's disease (AD), making Tau reduction a compelling therapeutic strategy. Although antisense oligonucleotides have shown promise, the need for repeated intrathecal administration and heterogenous CNS distribution represent potential challenges. A blood–brain barrier (BBB)-crossing adeno-associated virus (AAV) gene therapy offers the potential for more uniform CNS distribution and durable tau lowering with a one-time intravenous (IV) administration.
- VY1706 uses a proprietary BBB-crossing capsid to deliver a vectorized primary artificial microRNA (pri-amiRNA) targeting MAPT mRNA to the CNS. This capsid engages the vascular receptor alkaline phosphatase (ALPL) to enable efficient transport across the BBB, with substantially reduced biodistribution to the liver.
- ALPL is highly conserved across human, cynomolgus macaque, and mouse, with comparable relative expression in brain vasculature across these species, as well as in healthy vs AD disease states.
- VY1706 produced robust and dose-dependent reductions in MAPT mRNA, Tau protein, and pathological Tau across key brain regions in the P301S mouse model of tauopathy.
- In a non-GLP study in non-human primates (NHPs), single IV administration resulted in significant reductions in MAPT mRNA and Tau protein in AD-relevant brain regions at 11 weeks post-dose.
- In an IND-enabling GLP toxicology study in NHPs with 3-month and 6-month cohorts, VY1706 was evaluated across multiple dose levels, incorporating comprehensive investigation of biodistribution, pharmacology (MAPT mRNA and Tau protein lowering), safety pharmacology and histopathology.
- The findings presented here highlight the potential of VY1706 as a one-time gene therapy capable of achieving widespread CNS delivery and durable Tau lowering in AD-relevant brain regions with a favorable safety and tolerability profile, supporting its further development in the treatment of Alzheimer's disease.

Figure 1. VY1706, a Tau-lowering AAV Gene Therapy is Transported Across the BBB via the Highly Cross-species Conserved ALPL Receptor



VY1706-capsid mechanism and cross-species conservation. (**A**) Therapeutic goal and mechanism of action. (**B**) VY1706-capsid interacts with the highly conserved brain vascular receptor, ALPL to enable BBB-crossing. (**C**) Functional interaction of VY1706-capsid with ALPL across species. HEK293T cells transfected with indicated ALPL plasmid were transduced with AAV9- or VY1706-capsid luciferase. Data: mean ± SD luciferase activity normalized to control plasmid (n = 3). (**D**) Expression of ALPL protein in brain microvessels (BMVs), from proteomics analysis. Values indicate the percentile distribution of ALPL reads among the entire proteome. ALPL scored in approximately the 95th percentile of vascular protein reads in all three species, indicating high expression at the BBB, across species. Percentiles are plotted as mean ± SEM. N=3, 5, and 3 samples for mouse, cynomolgus macaque, and human, respectively. (**E**) Direct binding of VY1706-capsid to ALPL. Surface plasmon resonance (SPR) was used to characterize the binding kinetics of VY1706-capsid to mouse, cynomolgus macaque, and human ALPL and curve fits of the signals were used to calculate the equilibrium dissociation constant (KD). ALPL proteins were captured on the sensor chip and increasing concentrations of VY1706-capsid were applied as analytes.

Figure 2. VY1706 Shows Robust Tau Protein Knockdown in Neurons Across AD- and Primary Tauopathy-Relevant Brain Regions and is Liver Sparing in NHP Dose-range Finding Study



(**A–C**) Representative immunofluorescence images of Tau protein expression (green) in SMI311-positive neurons (magenta) from vehicle (**A**) and VY1706-treated (**B**) NHPs in the hippocampus at 11 weeks after VY1706 (1.3e13 VG/KG) administration. Scale bar = 500 µm. White box indicates inset of CA3 region shown below. Scale bar = 50 µm. Corresponding single channel representative images of inset show SMI311 protein (magenta, top) and Tau protein (green, bottom) immunofluorescence. Scale bar = 25 µm. Relative Tau immunofluorescence intensity in the SMI311 positive neuronal somata show a range of 41-78% reduction of tau immunoreactivity, relative to the vehicle group (relative neuronal Tau intensity [% of vehicle]) in all evaluated brain regions (**C**): entorhinal cortex (EC), hippocampus (HC), temporal cortex (TC), frontal cortex (FC), globus pallidus (GP), substantia nigra (SN), thalamus (TH) and pons (PO). The percentages shown above the bars are the mean percent lowering from vehicle for that group. Data are shown as the group mean ± SEM (N=6 for vehicle, and N=3 per treatment group). (**D**) VY1706 exhibited liver de-targeting compared to historical data on WT-AAV9 expressing an alternative transgene and dosed at 4E12 vg/kg.

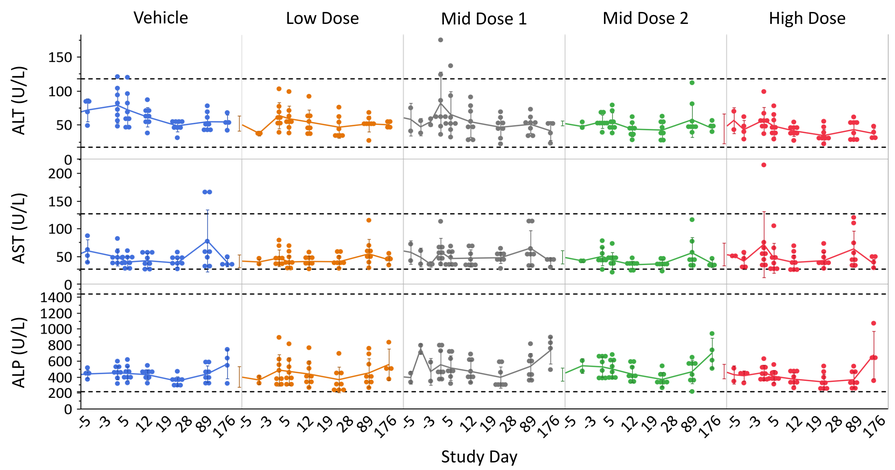
Table 1. Study Design of the VY1706 GLP Toxicology Testing Conducted in Cynomolgus Macaques

	Group	Route of administration	Number			
			3 Month Cohort		6 Month Cohort	
			Males (♂)	Females (♀)	Males (♂)	Females (♀)
VY1706	Vehicle	Single Intravenous infusion	2	2	2	2
	Low dose		2	2	2	2
	Mid dose 1		2	2	2	2
	Mid dose 2		2	2	2	2
	5E13 vg/kg		2	2	2	2

Immunosuppression: Daily oral methylprednisolone (Day -3, through 8 weeks, followed by tapering)

Study assessments: General toxicology, ophthalmic, cardiovascular and neurological safety pharmacology, histopathology, immunogenicity, biodistribution and pharmacology endpoints

Figure 3. VY1706 Shows No AAV-Typical Liver Transaminase Elevations at Any Dose Level Evaluated Through 6 Months



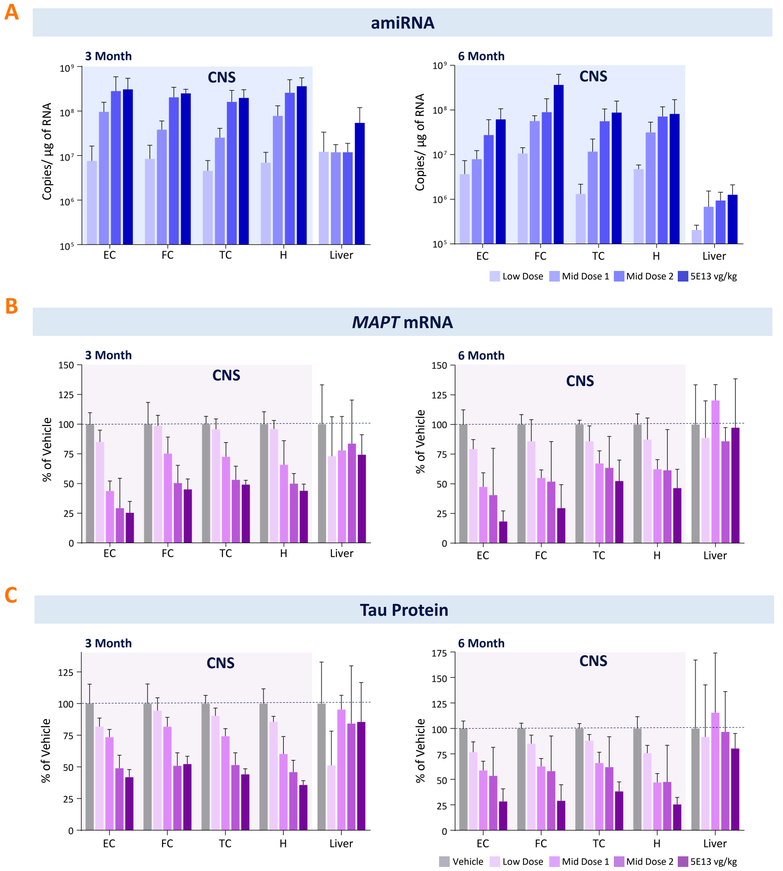
Representative liver function parameters (ALT: alanine aminotransferase, AST: aspartate aminotransferase & ALP: alkaline phosphatase) were evaluated as part of comprehensive serum clinical chemistry testing at following timepoints: Predose (multiple occasions), Post-dose Day 3, Day 5, Weeks 2, 4, 13 & 26. Broken horizontal lines in each panel bracket the typical normal range of these parameters for the test species. Data demonstrate absence of liver toxicity-associated serum level elevation of these parameters that are commonly reported with systemic AAV therapies, thereby corroborating the liver de-targeting property of capsid component of VY1706. Data are shown as mean ± SEM.

SUMMARY OF GLP TOX RESULTS

VY1706 was safe and well-tolerated with no adverse clinical pathology or histopathological findings in the CNS, DRGs, and peripheral organs up to the highest tested dose level of 5E13 vg/kg

- Well tolerated with no infusion reactions
- No gross pathology or organ weight findings
- No effects on clinical pathology parameters at any dose level (including liver)
- No adverse neurological, ocular, or cardiac safety findings
- No adverse DRG or neurological findings on histopathology or electrophysiology; plasma NfL was generally stable with no dose-related increases
- No cellular immune activation; TAb/NAb responses were typical of AAV

Figure 4. VY1706 Shows Dose-Dependent and Durable Increase in miRNA Level, Lowering of MAPT *mRNA* and Tau Protein in AD-relevant Brain Regions and is Liver Sparing in GLP NHP Toxicology Study



(**A**) Robust expression of VY1706 amiRNA was observed in the AD-relevant brain regions. Substantially lower level of VY1706 amiRNA expression was observed in liver compared to the brain regions. (**B**) VY1706 reduced MAPT mRNA expression across AD-relevant brain regions in a dose-dependent manner. No substantial or dose-dependent MAPT mRNA expression change was observed in the liver. (**C**) VY1706 lowered Tau protein levels in AD-relevant brain regions in a dose-dependent manner. n = 3-4/group; Plots show mean + SD. EC, entorhinal cortex; FC, frontal cortex; TC, temporal cortex; H, hippocampus.

CONCLUSIONS

- A single IV dose of VY1706 in NHPs achieved broad, durable, and dose-dependent CNS delivery with up to 75% lowering of MAPT mRNA and Tau protein in key Alzheimer's disease relevant brain regions through 6-months
- ALPL, a well conserved brain vasculature endothelial receptor, mediates VY1706 blood-brain barrier transport, supporting cross-species translatability
- VY1706 was safe and well-tolerated in the 3 and 6-month GLP NHP toxicology study, with no adverse clinical pathology or histopathological findings in the CNS, DRGs, and peripheral organs (including liver) up to the highest dose tested (5E13 vg/kg)
- Nonclinical package supports advancement to first-in-human evaluation in patients with Alzheimer's disease
- VY1706 IND is active and dosing in participants with early Alzheimer's disease is expected to begin in the second half of 2026