

Pharmacology and Safety Assessment of VY1706, a BBB-Crossing Tau-Lowering AAV Gene Therapy for Alzheimer’s Disease, in a GLP Toxicology Study in NHPs



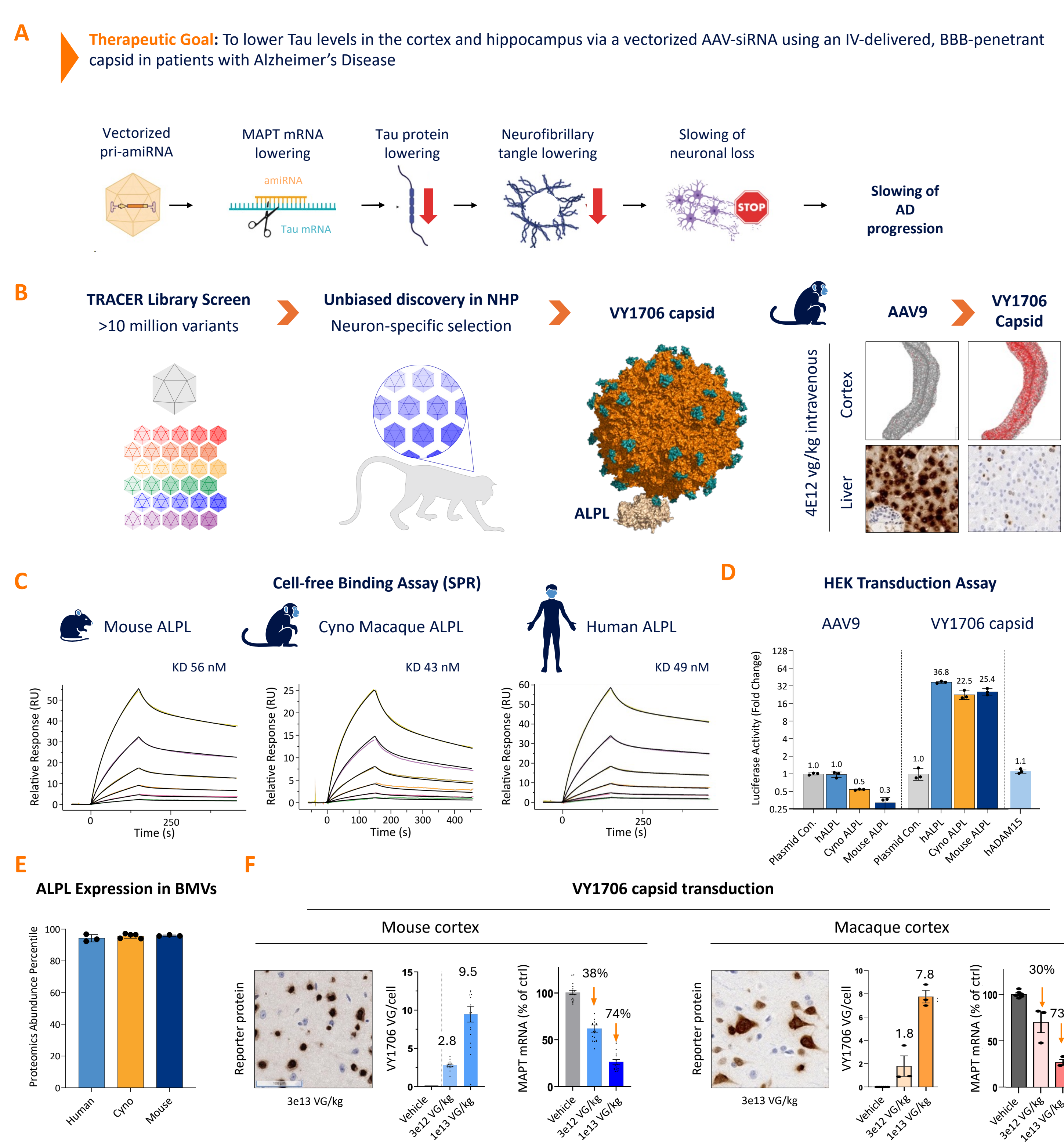
Vik Arora¹, Joydeep Ghosh¹, Yasuhiro Ito¹, Charlotte Chung¹, Wencheng Liu, Jeffrey Thompson¹, Hechen Bao¹, Cansu Colpan¹, Tyler Moyer¹, Brett Hoffman¹, Maneesha A. Paranjpe¹, Joydip Kundu¹, Su Jing Chan¹, Krishanu Mathur¹, Gonzalo Mile¹, Kevin Nguyen¹, Russ Udani¹, Patrick Carroll¹, Marina Feschenko¹, Sara Movassaghian¹, Robert Vass¹, Hima Ramachandradeddy¹, Camille Stengel¹, Kumar Dhanasekharan¹, Shamik Sharma¹, Tom Elch¹, Andrew Schrock¹, Bridget Shaughnessy¹, , Weitong Chen¹, Johnny Yao¹, **Mathieu Nonnenmacher¹**, Toby Ferguson¹, Elena Raffi¹, Dinah W.Y. Sah¹, Todd Carter¹, Rajeev Sivasankaran¹, Raj Rajagovindan¹

Voyager Therapeutics, Lexington, MA, USA

INTRODUCTION

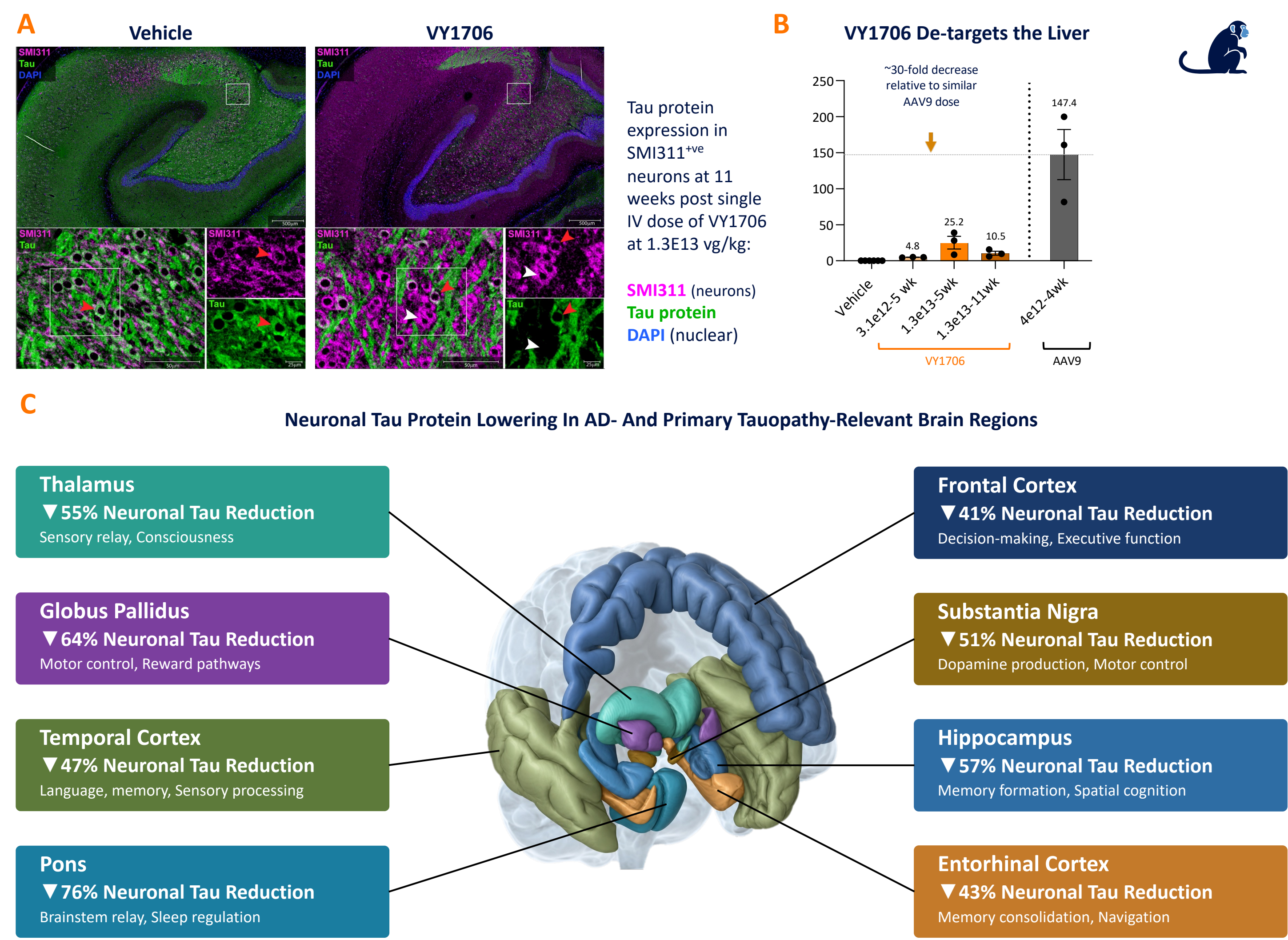
- Tau pathology is strongly linked to cognitive decline in Alzheimer’s disease (AD), making tau reduction a compelling therapeutic strategy. Although antisense oligonucleotides have shown promise, the need for repeated intrathecal administration and heterogeneous CNS distribution represents potential challenges. A blood–brain barrier (BBB)-crossing adeno-associated virus (AAV) gene therapy could enable more uniform CNS distribution and durable tau lowering following a one-time intravenous (IV) administration.
- To address this challenge, we engineered VY1706, which combines a proprietary BBB-crossing AAV capsid with a potent vectorized microRNA to lower MAPT mRNA in the CNS. Importantly, the VY1706 capsid engages alkaline phosphatase (ALPL) to enable efficient BBB transport in rodents and primates.
- Conserved ALPL sequence and tissue expression across species, together with similar capsid engagement of mouse, cynomolgus macaque, and human ALPL, support the translatability of VY1706 to humans. In a mouse model of tauopathy, VY1706 produced robust, dose-dependent reductions in MAPT mRNA, tau protein, and pathological tau across key brain regions.
- In nonhuman primates (NHPs), a single IV administration of VY1706 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, VY1706 was evaluated across multiple dose levels, with comprehensive assessment of biodistribution (vector genome and amiRNA levels), pharmacology (MAPT mRNA and tau protein lowering), and safety, including safety pharmacology endpoints.
- These results demonstrate favorable tolerability together with durable, dose-dependent tau lowering in AD-relevant brain regions. Collectively, these findings position VY1706 as a one-time gene therapy capable of achieving widespread CNS delivery and durable tau reduction, supporting its potential as a treatment strategy for 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) Evolution and characterization of VY1706 capsid, that interacts with the highly conserved brain vascular receptor ALPL to enable BBB-crossing. (C, D) Physical and functional interaction of VY1706 capsid with ALPL isoforms from various species measured by SPR (C) and transduction of HEK293T cells transfected with indicated control, ALPL or ADAM15 plasmids, measured by luciferase activity (D). (E) Comparative expression of ALPL protein in human, macaque and mouse brain microvessels (BMVs), from proteomics analysis. Values indicate the percentile distribution of ALPL reads among the entire proteome. ALPL scored ~95th percentile of protein reads in all three species, indicating high expression at the BBB. Percentiles are plotted as mean ± SEM (N=3). (F) Comparative dose-response of VY1706 capsid in mouse and macaques cortex, measured with 1) reporter protein expression at 3e13VG/kg (IHC, left panel), 2) viral genome biodistribution of VY1706 in the cortex at 3e12 and 1e13 VG/kg (middle panels) and 3) MAPT mRNA relative to vehicle control at 3e12 and 1e13 VG/kg (right panels).

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



VY1706 treatment allows widespread Tau reduction in NHP neurons. (A) Representative immunofluorescence images of Tau protein expression (green) in SMI311-positive neurons (magenta) from vehicle and VY1706-treated NHPs in the hippocampus at 11 weeks after VY1706 administration (1.3e13 VG/KG). 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. (B) VY1706 exhibited liver de-targeting compared to historical data on WT-AAV9 expressing an alternative transgene and dosed at 4E12 vg/kg. (C) Summarized reduction of Tau protein immunofluorescence intensity in the SMI311-positive neuronal somata relative to the vehicle group (relative neuronal Tau intensity [% of vehicle]) in brain regions relevant to Alzheimer’s disease: Data were collected from N=6 animals for vehicle group and N=3 for treatment group.

SUMMARY OF GLP TOX RESULTS

VY1706 was well-tolerated with no detectable 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 detected
- No detectable gross pathology or organ weight findings
- No effects on clinical pathology parameters were observed at the dose levels tested (including liver)
- No adverse neurological, ocular, or cardiac safety findings were observed at the dose levels tested
- No adverse DRG or neurological findings on histopathology or electrophysiology were detected; plasma NfL was generally stable with no dose-related increases
- No cellular immune activation; TAB/NAb responses were typical of AAV

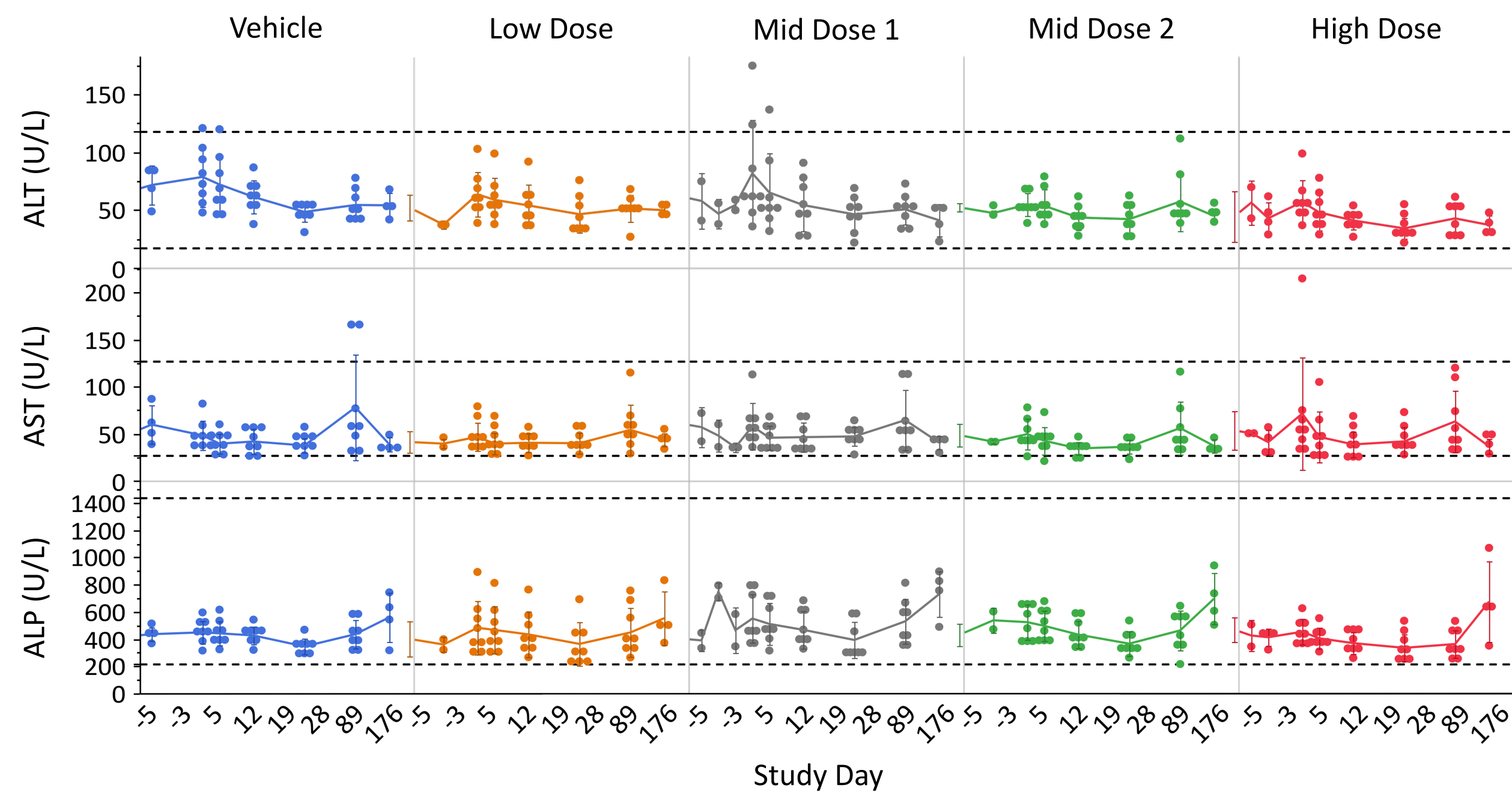
Table 1. Study Design of the VY1706 GLP Toxicology Testing Conducted in Cynomolgus Macaques

Group	Route of administration	Number			
		3 Month Cohort		6 Month Cohort	
		MALES (♂)	FEMALES (♀)	MALES (♂)	FEMALES (♀)
VY1706	Vehicle	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 the 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.

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 well-tolerated in the 3 and 6-month GLP NHP toxicology study, with no detectable 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 fourth quarter of 2026, pending patient enrollment.