Pharmacokinetics and Tolerability of VY-TAU01, an Anti-tau Antibody for the Treatment of Alzheimer's Disease, in P301s Mouse and Nonhuman Primate

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INTRODUCTION

Objectives

VY-TAU01 is a recombinant humanized IgG4 monoclonal antibody (mAb) directed against pathological tau that is intended to be administered via intravenous (IV) infusion to patients with mild dementia or mild cognitive impairment due to Alzheimer's disease (AD). VY-TAU01 specifically targets an epitope in the C-terminus of tau and is derived from the mouse IgG1 mAb Ab-01. VY-TAU01 binds to pathological tau with high affinity and selectivity over wild-type tau, blocks paired helical filaments seed-induced tau aggregates *in vitro*, and selectively stains tau tangles in AD and P301S mouse (C57/B6J-Tg[Thy1-MAPT*P301S]2541Godt) brain.

Nonclinical studies to support the initiation of the first-in-human study have been conducted in P301S mice and nonhuman primates (NHP). Here we describe the pharmacokinetics (PK) and tolerability of Ab-01 in P301S mice and VY-TAU01 in NHP.

Methods

1. Characterizing the PK and tolerability of Ab-01 in the P301S mouse after 5 weekly IV doses at 40, 80 or 120 mg/kg.
2. Characterizing the PK and tolerability of VY-TAU01 in NHP after a single IV dose at a high or mid dose level.

Results

No adverse effects were observed in P301S mice or NHP following Ab-01 or VY-TAU01 administration, respectively. The serum PK of 80 mg/kg Ab-01 in the P301S mouse exhibited a profile expected from a mouse IgG1 antibody with a half-life of approximately 12.6 days. Model based PK parameter estimates yielded a clearance rate (CL) of 0.166 mL/day, and central and peripheral volumes of distribution were 0.839 mL and 1.87 mL, respectively. Additional serum and cerebrospinal fluid PK results will also be presented.

Conclusions

Initial studies demonstrated that Ab-01 and VY-TAU01 are well-tolerated in P301S mice and NHP, respectively, and that the serum PK profile is as expected.

PROCEDURE

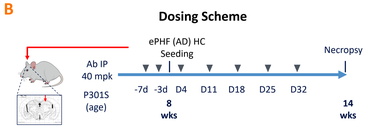
The ELISA methods for measurement of Ab-01 concentrations in mouse serum and CSF and VY-TAU01 concentrations in NHP serum and CSF were based on the high affinity of Ab-01 and VY-TAU01 binding to the C-terminal tau peptide that contains the phospho-epitope recognized by Ab-01. Biotinylated tau peptide containing the Ab-01 epitope was used for capture and horseradish peroxidase (HRP)-labeled goat anti-mouse IgG or mouse anti-human IgG4 was used for detection of Ab-01 or VY-TAU01, respectively. ELISA methods were fully validated at QPS, LLC.

Figure 1. P301S Seeding Model Treated with Murine Anti-tau Antibodies

A

Property	Criteria	Ab-01	Ab-04
Affinity to iPHF (Biacore)	nM	<0.06	0.12
Affinity to iPHF (Octet)	nM	0.26	2.75
Affinity to WT rec. Tau (Octect)	(nM)	>218	>218
Inhibition of seeding in biosensor Cells with ePHF	≤ 20 nM IC_{50}	16.3	18.6

B



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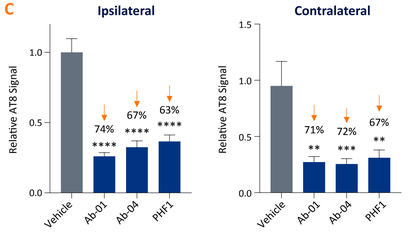

Efficacy of Ab-01 and Ab-04 in the P301S mouse hippocampal seeding model. (**A**) Biochemical and *in vitro* functional properties of Ab-01 and Ab-04 murine antibodies. (**B**) Study Design: Ab-01, Ab-04, and PHF1 (positive control) were IP administered at 40 mg/kg starting one week before ePHF seeding (2 doses) and then weekly for 5 additional doses after ePHF seeding. Vehicle, as a negative control, was IP injected using the same schedule. Six weeks after ePHF seeding and 10 days following the final administration of antibody or vehicle, hippocampi ipsilateral and contralateral to the side of seeding were isolated to measure levels of p-tau. (**C**) Levels of p-tau were measured by AT8 ELISA in the hippocampus ipsilateral and contralateral to the site of injection of ePHF and normalized to the average signal in the vehicle group (Relative AT8 Signal). There was a significant reduction in accumulation of p-tau in both ipsilateral and contralateral hippocampus with Ab-01 treatment, as well as with Ab-04 and PHF1 treatments, relative to the vehicle group. Statistical significance was evaluated with a one-way ANOVA with Tukey's multiple comparisons post-hoc test; **, *** and **** indicate $p < 0.005$, 0.0005 and 0.0001, respectively, compared to the vehicle control group. Data are shown as the group mean ± SEM. n = 18-20 per group.

Figure 2. Biochemical and Biophysical Properties of VY-TAU01 (Humanized Ab-01)

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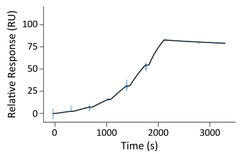

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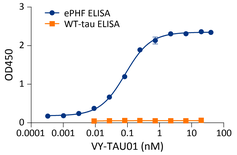

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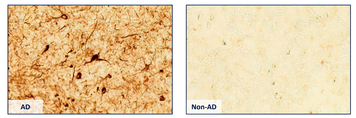

D

Property	VY-TAU01
Affinity to iPHF (Biacore, pM)	43.4
Affinity to ePHF EC_{50} (nM)	0.085
Selectivity: ePHF:WT rec. Tau[a]	>232.9
IHC Fixed - Human AD Brain	Positive
IHC Fixed - Human Ctl Brain	Negative
Western Frozen - Human AD Brain	Positive
Western Frozen - Human Ctl Brain	Negative
Inhibition of ePHF seeding in Biosensor Cells	50.3
Low Polyspecificity (using BVP ELISA)	1.7
PTM liability	0.505
Predict aggregation	Inc.

Biophysical characteristics of VY-TAU01. (**A**) VY-TAU01 binds selectively to immunopurified PHF tau with high affinity (K_D=43.4 pM) using Surface Plasmon Resonance (SPR) on Biacore 8K instrument. (**B**) Potency and selectivity of VY-TAU01 binding to ePHF. VY-TAU01 binds ePHF with an EC_{50} of 85.8 pM but not WT-tau. (**C**) VY-TAU01 Abs bind specifically to tau pathology in cortical sections from AD but not age-matched control brain. Note that AD and control cortical sections were provided by Banner Sun Health Research Institute, Sun City, AZ. (**D**) Summary table of biochemical and biophysical properties of VY-TAU01.

Figure 4. A 5-Week Pharmacokinetic Study of Ab-01 by Intraperitoneal Injection in P301S Mice Followed by Up to 3-Week Observation Period

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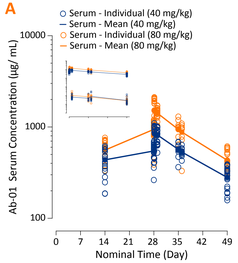

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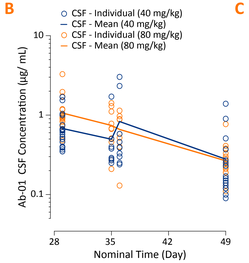

C

Dose Group	C_{max} (µg/mL)	T_{max}[a] (day)	CL_{ss}/F (mL/day/kg)	V_{ss}/F (mL/kg)	$T_{1/2,\lambda}$ (days)	AUC_{last} (day*µg /mL)	CSF:Serum AUC Ratio (%)
Serum							
40 mg/kg	844	0.125	8.03	151	13.00	4980	-
80 mg/kg	1510	0.125	9.38	157	11.62	8530	-
Cerebrospinal Fluid							
40 mg/kg	0.678	1.00	NC	NC	15.81	4.11	0.08
80 mg/kg	1.06	1.00	NC	NC	9.92	6.31	0.07

[a]T_{max} reported as median observed elapsed nominal time in days from last administered dose on Study Day 29.
C_{max}=maximum observed concentration; CL_{ss}/F = apparent systemic serum clearance at steady state after IP administration; V_{ss}/F = apparent volume of distribution during the terminal phase; AUC_{last}=area under the concentration-time curve over the dosing interval on Study Day 29 (time = 0 to 168h); NC=not calculated.

Serum and CSF PK of Ab-01 in P301S mouse with 5 weekly IP doses at 40 or 80 mg/kg (40 or 80 mg/kg QW x 5). Mean and individual (**A**) serum and (**B**) CSF Ab-01 concentrations vs. nominal time show no evidence of target-mediated disposition in either the serum or CSF. PK of Ab-01 were typical of mouse mAbs with linear PK behavior. (**C**) PK parameters were estimated using a naïve-pooled approach (mean averaged serum and CSF data by time point) using NCA to provide one PK parameter across the animals per matrix (serum or CSF). Absorption of Ab-01 from the intraperitoneal cavity into the systemic circulation appeared to be reasonably efficient in mice. There was an increase in systemic exposure in the 80 mg/kg group when compared to the 40 mg/kg group that appeared to be approximately dose proportional. The secondary estimated PK parameter $T_{1/2}$ (range 11.6 - 13.0 days) was typical of a mouse IgG1 administered to mice. Ab-01 steady state CSF to serum AUC ratio was approximately 0.07% and 0.08% in the 40 mg/kg and 80 mg/kg groups, respectively, and typical of mAb distribution to the CSF.

Figure 6. Summary of Pharmacokinetic Studies

Study	Dosing	CSF / Serum Ratio (%)	$T_{1/2}$, days	Concentration (mean), µg/ml
A 5-Week Pharmacokinetic Study of Ab-01 by Intravenous Injection in P301S Mice Followed by Up to 4-Week Observation Period	80mpk, 5xQ1W	0.146	12.8 (serum) 12.6 (CSF)	C_{max} Conc: 80 mpk: Serum => 3400 80 mpk: CSF=> 4.64
A 5-Week Pharmacokinetic Study of Ab-01 by Intraperitoneal Injection in P301S Mice Followed by Up to 3-Week Observation Period	40mpk 80mpk, 5xQ1W	0.08 0.07	Serum: 13 (40mpk) and 11.62 (80mPK) CSF:15.81 (40mpk) and 9.92 (80mpk)	C_{max} Conc: 40 mpk: Serum => 4980 40 mpk: CSF=> 4.11 80 mpk: Serum => 8530 80 mpk: CSF=> 6.31
Single Dose PK/tolerability Study of VY-TAU01 in Cynomolgus Monkey-IV Dosing	Mid and High Doses, single dose	0.186 (Mid Dose) 0.150 (High Dose)	Serum: 12.7 (Mid Dose) and 11.3 (High Dose) CSF: 7.98 (Mid Dose) and 10.5 (High Dose)	C_{max} Conc: Mid Dose: Serum=>2840, CSF=> 5.28 High Dose: Serum=> 8470, CSF=> 12.7

Figure 3. A 5-Week Pharmacokinetic Study of Ab-01 by Intravenous Injection in P301S Mice Followed by Up to 4-Week Observation Period

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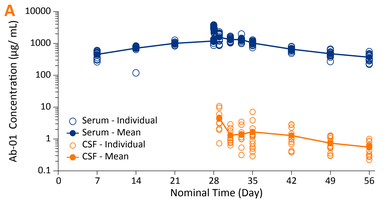

- No evidence of target-mediated disposition in either the serum or CSF.
- PK of Ab-01 is typical of mouse mAbs with linear PK behavior.

B

PK Parameters								
Matrix	C_{max} (µg/mL)	C_{last} (µg/mL)	T_{max}[a] (day)	CL_{ss} (mL/day/kg)	V_{ss} (mL/kg)	$T_{1/2,\lambda}$ (days)	AUC_{last} (day*µg/mL)	CSF:Serum AUC Ratio (%)
Serum	3400	369	28	8.03	135	12.8	9960	
CSF	4.64	0.554	28	NC	NC	12.6	14.5	0.146

[a]T_{last} given as elapsed nominal time in days from last administered dose on Study Day 29.
C_{max}=maximum observed concentration;
C_{last}=concentration at last measurable time point;
T_{last}=time of C_{last};
CL_{ss}=systemic serum clearance at steady state;
V_{ss}=steady-state volume of distribution;
AUC_{last}=area under the concentration-time curve over the dosing interval (time = 0 to Day 7);
NC=not calculated;
CSF=cerebrospinal fluid

Serum and cerebrospinal fluid (CSF) PK of Ab-01 in P301S mouse with 5 weekly IV doses at 80 mg/kg (80 mg/kg QW x 5). (**A**) Serum and CSF Ab-01 concentrations vs. nominal time. The Ab-01 PK profile in serum with IV dosing was characterized by a distribution phase followed by a typical elimination phase. Data show no evidence of target-mediated disposition in either the serum or CSF. The PK of Ab-01 was typical of mouse mAbs with linear PK behavior. (**B**) Serum and CSF PK parameters were estimated using a naïve-pooled approach (mean averaged serum and CSF data by time point) using noncompartmental analysis (NCA) to provide one PK parameter across the animals per matrix (serum or CSF). The primary serum derived Ab-01 PK parameters of CLss (8.03 mL/day/kg) and V_{ss} (135 mL/kg) and secondary parameter $T_{1/2}$ (12.8 days) were typical of a mouse IgG1 administered to mice. Ab-01 steady state CSF to serum AUC_{tau} ratio was approximately 0.15% of serum exposure, typical for mAb distribution to the CSF.

Figure 5. A 7-Week Pharmacokinetic Study of VY-TAU01 Following Intravenous Dosing with CSF Sampling via Intrathecal Catheter in Non-Human Primates

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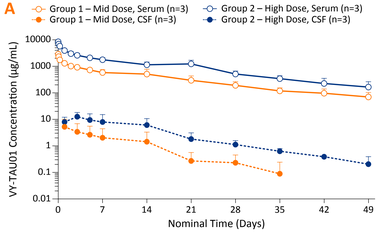

- VY-TAU01 appeared to exhibit linear PK in the serum.
- The serum C_{max} and AUC_{inf} increased in a dose proportional manner.
- VY-TAU01 CSF distribution was approximately 0.1 - 0.2% of serum exposure.

B

Serum						
	Parameter	$T_{1/2}$	C_{max}	AUC_{inf}	CL	Vss
	Parameter Unit	(day)	(µg/mL)	(day· µg/mL)	(mL/day)	(mL)
Group 1 Mid Dose	N	3	3	3	3	3
	Mean	12.7	2840	18700	14.5	238
	SD	1.61	192	5690	4.81	56.5
Group 2 High Dose	N	3	3	3	3	3
	Mean	11.3	8470	53200	16.2	251
	SD	2.29	468	13300	3.61	14.3

CSF				
	Parameter	$T_{1/2}$	C_{max}	AUC_{inf}
	Parameter Unit	(day)	(µg/mL)	(day· µg/mL)
Group 1 Mid Dose	N	3	3	3
	Mean	7.98	5.28	45.5
	SD	1.77	4.91	47.8
Group 2 High Dose	N	3	3	3
	Mean	10.5	12.7	167
	SD	3.61	5.60	101

Serum and CSF PK of VY-TAU01 in NHP with a single mid or high IV dose. (**A**) Mean serum and CSF VY-TAU01 concentration vs. time. (**B**) PK parameters were estimated by NCA. VY-TAU01 serum PK was dose proportional; no concentration-dependent PK was observed. Clearance (CL) and steady state apparent volume of distribution (Vss) parameters from the serum PK analysis were typical of a human IgG4 monoclonal antibody administered to a monkey, demonstrating modest clearance and a volume of distribution consistent with distribution to serum and interstitial fluid. The serum half-life was approximately 12 days. VY-TAU01 CSF distribution was approximately 0.1 - 0.2% of serum exposure, typical of mAb distribution to the CSF. The CSF half-life was approximately 9.2 days.

CONCLUSIONS

- Ab-01 and VY-TAU01 PK profiles in serum and CSF were characterized by a distribution phase followed by a typical elimination phase without evidence of substantial target-mediated disposition in the respective compartments.
- Serum and CSF concentrations increased with increasing dose levels in an approximately dose proportional manner.
- Half-lives of Ab-01 and VY-TAU01 in P301S mice and NHP, respectively, were approximately 9 to 13 days, as expected for mouse IgG1 and human IgG4 in their respective species.
- CSF concentrations were 0.1 - 0.2% of serum concentrations.
- There were no unexpected changes in exposure for Ab-01 in the P301S mouse or VY-TAU01 in the NHP that would indicate the presence of a PK-altering anti-drug antibody (ADA) response.
- Ab-01 and VY-TAU01 were well-tolerated in the P301S mouse and NHP, respectively.