Pharmacokinetics and Pharmacodynamics of an Antibody Targeting Pathological Tau for the Treatment of Alzheimer's Disease: Nonclinical Studies in P301S Mice and Cynomolgus Macaques

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INTRODUCTION

VY-TAU01 is a recombinant humanized IgG4 monoclonal antibody (mAb) directed against pathological tau for the treatment of patients with mild cognitive impairment or mild dementia due to Alzheimer's disease (AD). Both VY-TAU01 and its parental mouse IgG1 mAb Ab-01 target an epitope in the C-terminus of tau, bind pathological tau with high affinity and selectivity over wild-type tau, block paired helical filament seed-induced tau aggregates in vitro, and selectively stain tau tangles in AD and P301S mouse (C57/B6J-Tg[Thy1-MAPT*P301S]2541Godt) brain. Ab-01 robustly inhibits seeding and propagation of pathological tau in a P301S mouse seeding model.

To support toxicology studies and the initiation of the first-in-human study, nonclinical studies have been conducted to characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of Ab-01 in P301S mice and the PK of VY-TAU01 in cynomolgus macaques.

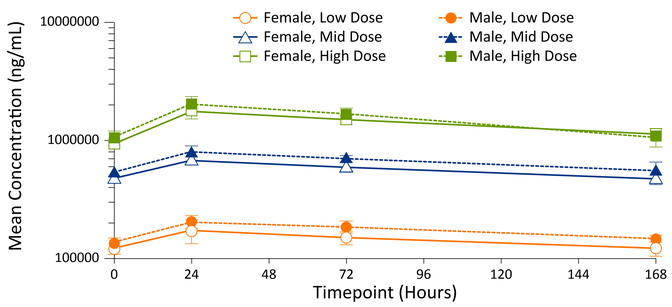
METHODS

- The PK of Ab-01 in the P301S mouse after 5 weekly intravenous or intraperitoneal doses at 10 to 120 mg/kg and VY-TAU01 in cynomolgus macaques after a single intravenous administration at mid or high doses as well as after five weekly administrations at low, mid, and high doses was evaluated with validated ELISAs using their target epitope peptide.
- The PD of Ab-01 in the P301S mouse was also evaluated using an ELISA to quantify unbound p-Tau target levels.

RESULTS

Ab-01 and VY-TAU01 PK profiles in serum and cerebrospinal fluid (CSF) were characterized by a distribution phase followed by a typical elimination phase in the respective compartments. Serum and CSF concentrations increased with increasing dose levels in an approximately dose proportional manner, and their half-lives were approximately 9 to 13 days. CSF concentrations of both antibodies were 0.1 - 0.2% of their corresponding serum concentrations.

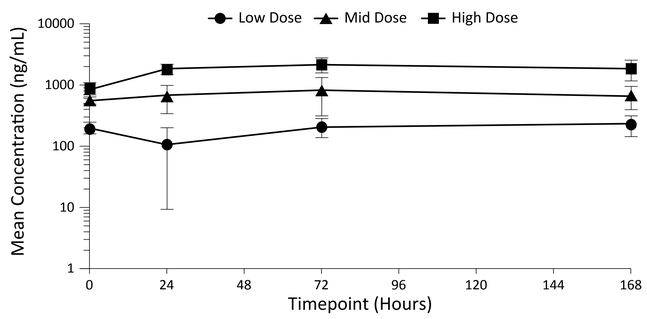
Figure 1. Serum Concentration vs. Time Curves for Ab-01 in Male and Female P301S Mouse Following IV Bolus Administration



Mean (± SD) serum concentration vs. time curves for Ab-01 in male and female P301S mouse following IV bolus administration of Ab-01 on Day 29 (Log : Linear).

Ab-01 was quantifiable in the P301S mice throughout the 168-hour sampling period on Day 29, and t_{max} values for Ab-01 in serum concentrations were observed by 24 hours postdose on Day 29 at all dose levels. Following weekly IV bolus administration of Ab-01 to the P301S mice, C_{max} and $AUC_{0\text{-}168hr}$ values of Ab-01 increased with increasing dose on Day 29. On Day 29, a 12-fold increase in Ab-01 dose from 10 to 120 mg/kg/dose resulted in an approximate 10-fold increase in Ab-01 C_{max} values and an approximate 9.34-fold increase in Ab-01 $AUC_{0\text{-}168hr}$ values. Systemic exposure to Ab-01 was independent of sex. Individual serum concentration-time profiles, C_{max}, and AUC values were similar between males and females (F:M C_{max} ratios ranged from 0.843 to 0.877 and F:M $AUC_{0\text{-}168hr}$ ratios ranged from 0.828 to 0.919).

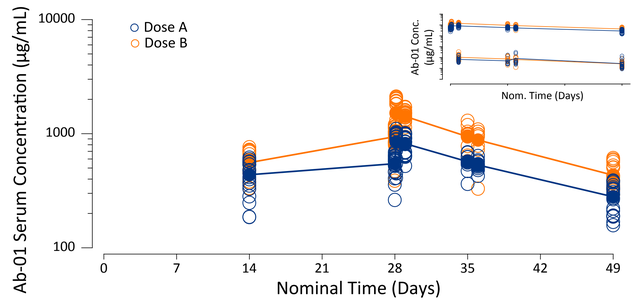
Figure 2. CSF Concentration vs. Time Curves for Ab-01 in Male and Female P301S Mouse Following IV Bolus Administration



Mean (± SD) CSF concentration vs. time curves for Ab-01 in male and female P301S mouse following IV bolus administration of Ab-01 on Day 29 (Log : Linear).

Ab-01 was quantifiable in male and female P301S mouse CSF throughout the 168-hour sampling period. Mean CSF concentrations of Ab-01 increased with increasing dose from 10 to 120 mg/kg/dose for both sexes, and comparable CSF concentration values were observed in females and males at all dose levels. The mean serum concentration values of Ab-01 were approximately 1000-fold higher than in CSF on Day 29 at all dose levels.

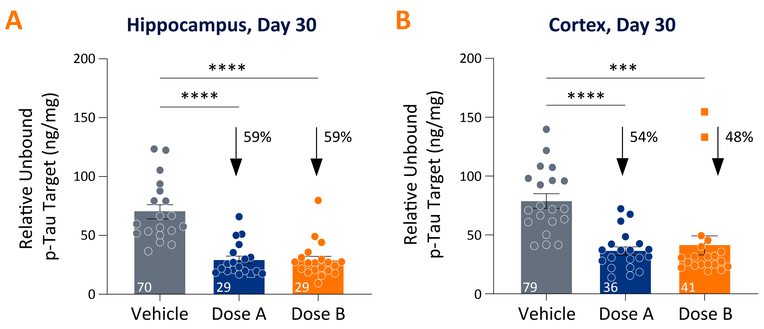
Figure 3. Serum and CSF Concentration vs. Time Curves for Ab-01 in Male and Female P301S Mouse Following Weekly IP Administration



Mean and individual serum and cerebrospinal fluid (CSF) Ab-01 concentrations vs. nominal time following weekly IP administration of Ab-01 (two dose levels, QW x 5). Inset plot shows Nominal Day 28 – Day 49 Ab-01 CSF and serum concentrations on the same scale (lower, CSF; upper, serum).

The PK / PD relationship of Ab-01 in the P301S mouse was also evaluated. For PD assessment, levels of free pTau target (i.e., Ab-01-unbound) were measured in the mouse brain hippocampus and cortex lysates using an ELISA.

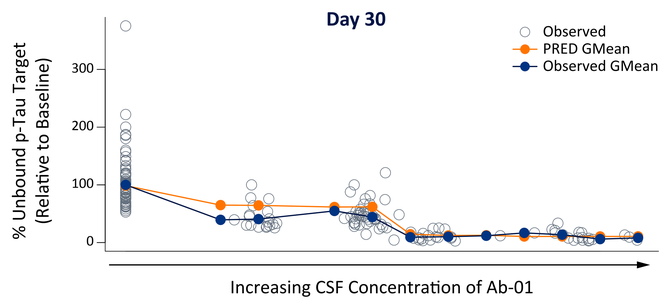
Figure 4. Reduction of Unbound p-Tau Target Levels in the Hippocampus and Cortex of P301S Mice Treated with Ab-01 on Day 30



Significant lowering of unbound p-Tau target on Day 30 in P301S mouse hippocampus and cortex after treatment with Ab-01. Equal number of male and female P301S mice were injected with 2 dose levels of Ab-01 weekly for a total of 5 IP doses before tissue collection on Day 30 approximately 24 hours after the final dose. The P1 fraction of tissue homogenates of (**A**) hippocampus and (**B**) cortex were assayed in duplicate with an ELISA using the target epitope peptide. Each data point represents the mean value of assay duplicates from a single animal; circles are values determined within the quantifiable range of the assay and squares are the assigned lower or upper values for those samples that are BLOQ or above the ULOQ, respectively. The bar graphs show the mean value of the groups ± standard error of the mean (SEM). The group mean is shown within each column. N=19-20 / group. Statistical analyses were performed using one-way ANOVA with Dunnett's multiple comparisons test. **** $p < 0.0001$, *** $p = 0.0002$.

Based on the PK and PD data described above and from several other studies, we developed population PK models using serum and cerebrospinal fluid (CSF) concentrations of Ab-01 in P301S mice. Population PK models were fit to serum and CSF concentrations of Ab-01 in P301S mice from 5 preclinical studies, and a visual prediction check showed good concordance between the model and the observed dataset. Following selection of the P301S mouse PK model, a population PK/PD model was then developed to describe the relationship between levels of unbound p-Tau target in P301S mouse hippocampus and predicted Ab-01 concentrations in CSF using the observed unbound p-Tau target levels in P301S mice from 3 preclinical studies. The ability of the PK/PD model to describe the observed data was evaluated with goodness-of-fit (GOF) plots and model fit was confirmed using concordance and residual diagnostic plots.

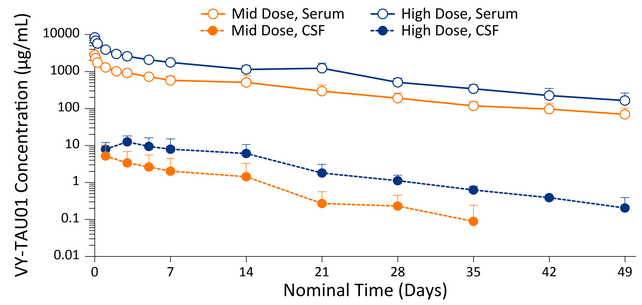
Figure 5. PK/PD Model: P301S Mice Treated with Ab-01



The GOF plot depicts the central tendency of model-predicted response overlaid on the observed concentration-response profile. Overall, this plot shows general concordance with central tendency (geometric mean) of observed and population predicted (PRED) responses, which suggests the model is able to adequately describe the observed data. However, the model was not able to estimate EC50 for Ab-01 in P301S mice due to sparse data around the suspected range of this parameter. ICSF, Individual Predicted CSF concentration; PRED, Population prediction; Gmean, Geometric mean.

To support the initiation of the first-in-human study, additional nonclinical studies have been conducted to characterize the PK of VY-TAU01 in cynomolgus macaques with a single dose or five weekly doses.

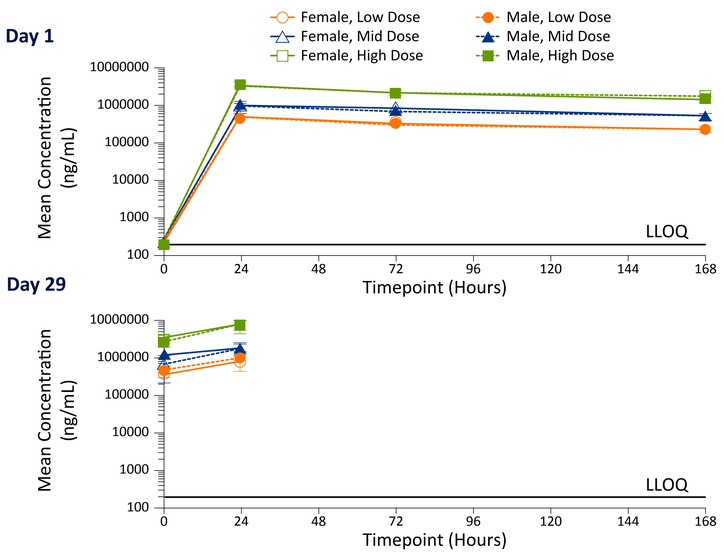
Figure 6. Serum Concentration vs. Time Curves for VY-TAU01 in NHP Serum and CSF Following a Single IV Administration



Mean (SD) serum and CSF VY-TAU01 concentration vs. time following a single intravenous administration of VY-TAU01 by dose group (N = 3 for each cohort).

The VY-TAU01 PK profile in serum after administration of either a mid or high dose by infusion over 15 minutes was characterized by a distribution phase followed by a typical elimination phase without evidence of target-mediated elimination in the concentration-time profile. At the high dose, pseudo-equilibration with the serum was observed at 72 hours compared to 24 hours at the mid dose. VY-TAU01 appeared to exhibit linear PK in the serum, consistent with the concentration-time profiles over this dose range. The serum C_{max} and AUC_{inf} increased in a dose proportional manner. VY-TAU01 mean CSF concentrations were approximately 0.1% of the serum concentration and the decline in the CSF paralleled the serum concentrations as expected for a monoclonal antibody.

Figure 7. Serum VY-TAU01 Concentrations in Male and Female Cynomolgus Macaque Following a Single IV Dose (Day 1) or 5 Consecutive Weekly IV Doses (Day 29)



Semi-log plot of mean ± standard deviation VY-TAU01 concentrations in male and female cynomolgus macaque serum following a single IV dose (Day 1) or 5 consecutive weekly IV doses (Day 29) of low, mid, or high dose VY-TAU01.

Following a single or 5 consecutive weekly IV doses of VY-TAU01, peak exposure was at the first post-dose testing timepoint (24 hr). There were no overt sex differences observed in VY-TAU01 PK. Total serum exposure following single or repeated IV dosing was overall dose proportional across the VY-TAU01 dose range evaluated. Serum VY-TAU01 accumulation was observed after 5 consecutive weekly doses. Accumulation was also observed in peak exposure as quantified by dose-normalized C_{max}. Total exposure as quantified by dose-normalized $AUC_{0\text{-}24hr}$ was not substantially different for 5 consecutive weekly doses compared to a single dose (ratios greater than 1 but less than 2-fold changed). Serum accumulation of VY-TAU01 suggested the lack of any substantial PK-altering anti-drug antibody formation in cynomolgus monkey up to Day 30.

CONCLUSIONS

- The PK of Ab-01 in the P301S mouse and VY-TAU01 in the cynomolgus macaque, and CSF to serum ratios were typical of murine IgG1 and human IgG4 administered to these respective species.
- The PD of Ab-01 in the P301S mouse demonstrated robust lowering of unbound p-tau target.
- The PK/PD model was used to project doses for the first-in-human (FIH), single ascending dose clinical trial of VY-TAU01 that provide substantial exposure margins over the NOAELs in GLP toxicology studies and encompass dose levels that are predicted to provide CSF exposures that result in up to 90% p-tau target reduction.
- Data from the on-going FIH study will be used to confirm the PK and exposure projections.