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

INTRODUCTION

VY-TAU01 is a recombinant humanised IgG4 monoclonal antibody (mAb) directed against pathological tau that is intended to be administered via intravenous (IV) infusion to patients with mild to mild-moderate 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 destabilized tau aggregation in vitro, and selectively stains tau tangles in AD and P301s mouse (C57Bl6/Sy/Tg-VMP1P301S541L(D8B)) 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 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 half-life with a half-life of approximately 12.6 days. Model-based PK parameter estimates yielded a clearance rate (CL) of 0.156 mL/day, and central and peripheral volumes of distribution were 0.839 mL and 1.87 mL, respectively. Additional serum and cerebrospinal fluid (CSF) 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.

PROCEEDURE

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 phosphorylation epitope recognized by AB-01. Biodistributed tau peptide containing the AB01 epitope was used for capture and horseradish peroxidase (HRP)-labeled goat anti-mouse IgG or mouse anti-human IgG was used for detection of AB-01 or VY- TAU01, respectively. ELISA methods were fully validated at QDS, LLC.

Figure 1: P301s Seeding Model Treated with Murine Anti-tau Antibodies

Figure 2: Biological and Biophysical Properties of VY-TAU01 (Humanized Ab-01)

Figure 3: A 5-Week Pharmacokinetic Study of Ab-01 by Intraperitoneal Injection in P301s Mice Followed by Up to 4-Week Observation Period

Figure 4: A 5-Week Pharmacokinetic Study of Ab-01 by Intraperitoneal Injection in P301s Mice Followed by Up to 3-Week Observation Period

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

Figure 6: Summary of Pharmacokinetic Studies

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 in P301s mice and NHP, respectively, were approximately 9 to 13 days, as expected for mouse IgG3 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 P-gp-antagonizing drug antibody (ADA) response.
- Ab-01 and VY-TAU01 were well-tolerated in the P301s mouse and NHP, respectively.