BACKGROUND

Alzheimer's disease (AD) is a progressive neurodegenerative disease that clinically presents as a gradual onset of dementia, beginning with mild cognitive and functional deficits, leading eventually to inability to carry out everyday tasks.

Recent postmortem evidence in AD pathology indicates amyloid-β (Aβ) and tau. Multifocal and abnormally phosphorylated aggregates of tau protein are the principal pathological components in neurofibrillary tangles. The spread of tau pathology through the brain follows a predictable spatiotemporal pattern and is associated with progressive cognitive decline in AD.

Evidence indicates that tau pathology may propagate through cell-to-cell communication, spreading locally and between interconnected regions of the brain. The extent of tau pathology detected by positron emission tomography (PET) correlates with amyloid and cognitive decline.

The microtubule-binding region (MTBR) is a primary component of tau, which plays a significant role in the progression of AD. Several reports have confirmed the importance of the MTBR in tau pathology:


The primary objective was to characterize the safety, tolerability, and immunogenicity of PRX005 when administered intravenously (IV) as a single dose in healthy volunteers.

The secondary objective was to evaluate the plasma pharmacokinetics (PK) and CSF profile of PRX005.

METHODS

- **Healthy volunteers received a single IV dose of PRX005 in 3 cohorts.**
- **Safety data and plasma samples were collected during all study visits up to 2 months.**
- **Key exclusion and criteria are shown in Table 1.**

OBJECTIVES

The data presented here summarize results from the single ascending dose portion of the first-in-human Phase 1 clinical trial of PRX005, a humanized IgG1 monoclonal antibody that binds to the MTBR of tau with high affinity to the R1, R2, and R3 repeats in the MTBR of tau, and targets both R2 and R3 repeats.

RESULTS

**Demographics and Baseline Characteristics**

- **A total of 25 subjects were randomized and dosed in the study (safety population).**
- **8 subjects were enrolled in PRX005 (3 cohorts):**
  - Low dose cohort S1 (n=6)
  - Medium dose cohort S2 (n=7)
  - Combined cohort S3 (n=19)

- **One subject in the PRX005 low-dose group withdrew early due to a treatment-emergent adverse event (TEAE) that was not considered related to study drug.**

**RESULTS (CONTINUED)**

**PK and Anti-Drug Antibody (ADA) Results**

- Results from the PRX005 low-dose safety population study suggests a good profile of safety and tolerability. The CSF levels after a single dose predict sufficient exposure for saturation of CNS target engagement for >28 days (CSF plasma ratio) of the ongoing clinical trial.

- No anti-drug antibodies (ADAs) were observed following treatment with PRX005.

**Safety Results**

- Two of 10 placebo-treated subjects (33.3%) and 10 of 19 PRX005-treated subjects (52.6%) experienced at least one TEAE.

**CONCLUSIONS**

We present results from the safety population of a single ascending dose cohort of PRX005 in an ongoing, multiple ascending dose study in patients with AD.

**Support:**