Interim Safety and Biomarker Analysis of PRECISE-AD

William G. Mantyh[1], Wendy Luca[2], Misty Lamendola[2], Heidi Pavia[2], Lindsay Moody[2] ,Neil Warma[2], Max Milbury[2], Johanne Kaplan[2], Suzanne Hendrix[3], Larry Altstiel[2], Neil Cashman[1,4]

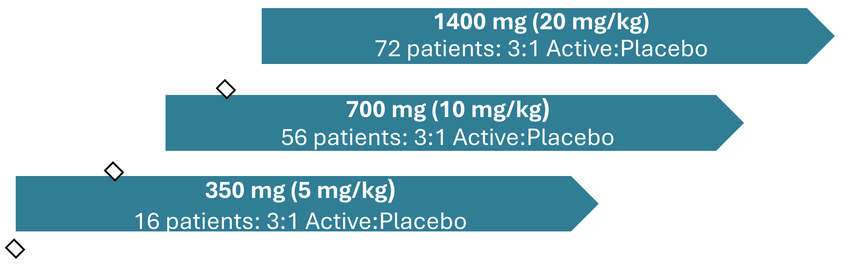
[1]University of Minnesota, [2]Promis Neurosciences, [3]Pentara, [4] University of British Columbia

Background: Low molecular weight soluble Aβ oligomers (ABO) formed from misfolded Aβ are a key neurotoxic species responsible for synapse damage, promotion of abnormal tau phosphorylation, neuroinflammation, and direct neuronal toxicity. PMN310 is a humanized IgG1 monoclonal antibody that recognizes a specific 3-dimensional epitope in misfolded Aβ. It binds to ABO with sub-nanomolar affinity; and does not bind to either amyloid plaque or Aβ monomers. Therefore, PMN310 may inhibit ABO activity and facilitate its removal. PMN310 is currently being evaluated for safety, target engagement, and preliminary efficacy in a Phase 1b study, PRECISE-AD (NCT06105528**).**

Methods:

Patient population: Mild Cognitive Impairment (MCI due to AD), Mild AD dementia, MMSE 20-28. Diagnosis confirmed by clinical criteria and amyloid PET.

Study design: Multiple ascending dose; 12 monthly i.v. infusions. 3:1 active:placebo randomization in each arm.



Total enrolled: 144 patients

Safety-evaluable: 136 patients

Mean age: 73.3 years
Sex: 58% women, 42% men
Race: White 69%, Hispanic 24%, Black 6%, Asian 1%
APOE4 carriers: 50% heterozygotes, 11% homozygotes

Safety outcomes: ARIA-E, ARIA-H incidence. Infusion reactions SAEs
Biomarker outcomes: plasma; pT217, GFAP, NfL, Aβ42/40, CSF; neurogranin, SNAP-25, NfL, Aβ42/40, MTBR-tau243, pT217, Alamar neurodegeneration and neuroinflammation panels
Cognitive outcomes: iADRS, CDR-SB, ADAS-cog, CGIC, MMSE, ADCS-iADL

Analysis: We conducted an interim blinded analysis for trends in safety and selected biomarker outcomes for all patients in the study who had ≥ 24 weeks of treatment. Data were analyzed in aggregate, and no attempt was made to separate patients based on treatment assignment or other criteria. Clinical outcome data were not analyzed. ARIA and other safety results are continuously assessed throughout the trial and include all patients in the study from baseline to 6 months. Biomarker data are based on week 24 completion.

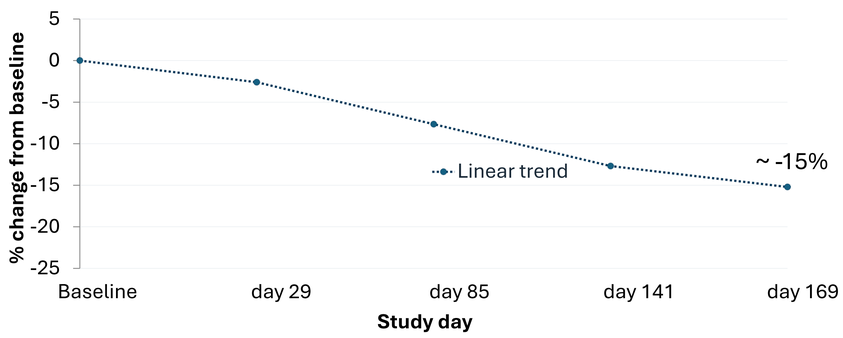
Results:

Interim blinded safety analysis:

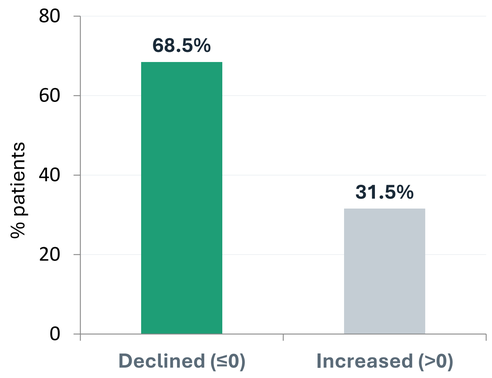
- ***0.0% ARIA-E*** Based on this sample size, we can estimate with 95% confidence that the true ARIA-E incidence rate in this population is currently no higher than 2.7%, comparing favorably to established ARIA-E rates for existing plaque removing therapies
- ***4.4% ARIA-H*:** All mild radiographic intensity and asymptomatic, no change in dosing, comparable to placebo rate in published studies
- ***No treatment-related SAEs***
- ***No treatment-related discontinuations***
- ***Minimal infusion reactions*:** 1 non-serious infusion reaction with no change in dosing

Interim blinded analysis: 6-month plasma pT217; CSF MTBRtau243

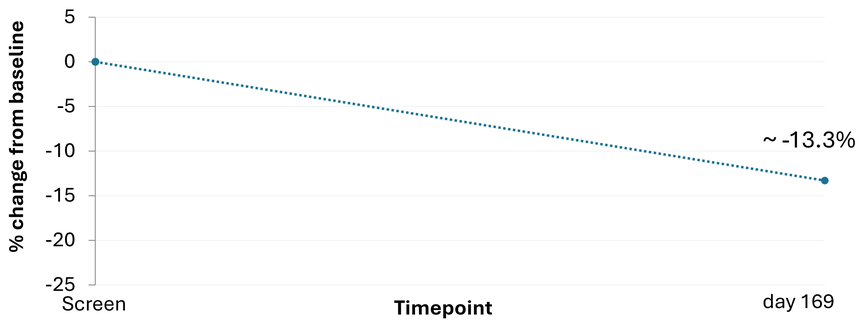
Mean % change in plasma pT217 from baseline over time in blinded patient population



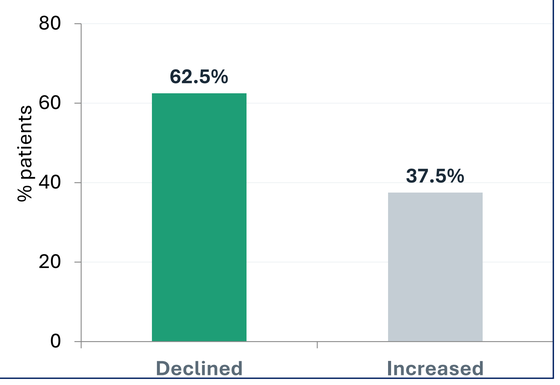
Blinded patients with a baseline to day-169 decline or increase in plasma pT217



Mean % change in CSF MTBR tau243 from baseline to 6 months in blinded patient population



Blinded patients with a baseline to day-169 decline or increase in CSF MTBRtau243



Conclusion:

These interim results neither represent nor predict the final study outcome. Nevertheless, they do suggest PMN310 has a favorable safety profile in this patient population. Greater than 90% of ARIA-E associated with current therapies occurs within 6 months of treatment. The absence of ARIA-E in 136 patients evaluated in the PRECISE-AD study to date is likely because PMN310 does not bind to fibrillar amyloid and therefore cannot interact with vascular amyloid deposits. The 4.4% rate of ARIA-H is consistent with the placebo ARIA-H rate in published studies and may represent the spontaneous microvascular hemorrhage rate observed due to cerebral amyloid angiopathy in AD patients. *APOE4* gene dosage significantly increases the risk of clinically relevant treatment-related ARIA-E for plaque removing monoclonal antibodies. The absence of ARIA-E suggests that *APOE* genotype may not influence ARIA-E for participants in this study. Infusion reactions (< 1%) were minimal compared with current therapies.

The preliminary, pooled biomarker trends may indicate the ability of PMN310 to inhibit ABO activity and reduce ABO concentration thereby reducing the abnormal phosphorylation of tau. Unblinded, placebo-controlled analyses are required to formally establish pharmacodynamic target engagement. The proportion of patients demonstrating a biomarker decline roughly aligns with the trial's 3:1 (active to placebo) randomization schedule. However, individual variations in disease trajectory and potential placebo effects must be considered until the data are unblinded.

The safety data indicate that PMN310 is well tolerated and may have a significantly reduced ARIA-E liability and improved tolerability compared to existing therapies. The biomarker data suggest pharmacodynamic target engagement.