PRECISE-AD, A Phase 1b, Double-Blind, Placebo-Controlled, Multiple Ascending Dose Study of the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Preliminary Efficacy of PMN310 in Patients with Early Alzheimer's Disease

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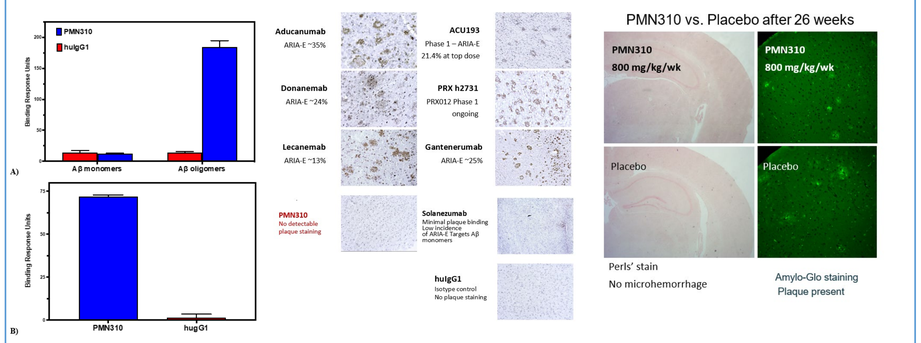
Background

Toxic Aβ oligomers (AβO) are implicated in the progression of Alzheimer's disease (AD). PMN310 is a humanized IgG1 monoclonal antibody that binds to a computationally derived three-dimensional epitope specific to misfolded Aβ in AβO. It binds only to AβO and not to Aβ monomer or plaque. Because PMN310 inhibits toxicity of AβO and does not bind to plaque, thereby potentially limiting risk of ARIA, it is being developed as a therapy for early AD.



A) PMN310 preferentially binds AβO **PMN310 does not bind to plaque** [2] **PMN310 does not cause microhemorrhage**
B) PMN310 binds to synthetic AβO[2] **In transgenic mouse model[2]**
& AβO in soluble AD brain fraction[1]

Phase 1a Study showed PMN310 had dose –proportional CSF levels sufficient to engage target

PMN310 CSF concentration measured 3 and 29 days after dose.

Molar [PMN310] >> [AβO] over all dose ranges.

Day: Day 3 Day 29

CSF $t_{1/2}$ ≈ 28 days

Methods

PRECISE-AD, NCT06750432, is a double blind, placebo-controlled, multiple-ascending dose study of PMN310 to evaluate safety, tolerability, PK, PD, and preliminary efficacy of multiple intravenous infusions of PMN310 in patients with early Alzheimer's disease.

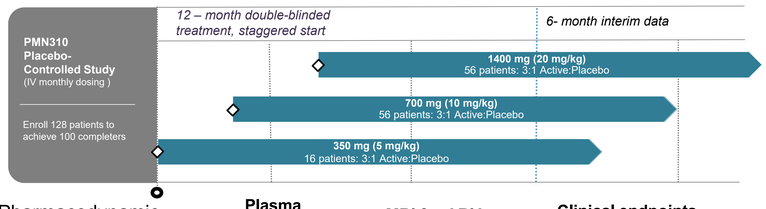
- The study consists of three staggered dosing arms with 12 monthly doses of PMN310 350 mg, 700 mg, 1400 mg.
- Patients are randomized 3:1, PMN310: placebo and receive either PMN310 or placebo once every 28 days for a total of 12 infusions.
- The study will enroll 128 patients with either Stage 3 or 4 AD.
- Diagnosis is determined by clinical criteria, plasma biomarkers, Aβ PET.
- MRI scans are done at baseline and weeks 6,14, 24, 30, 38, 46, 52 to detect potential ARIA.
- Plasma biomarkers (pTau217, GFAP, Aβ42/Aβ40, NfL) are measured at baseline and at 3-month intervals.
- Biomarkers in CSF (pTau217, pTau 243, GFAP, SNAP25, neurogranin, Aβ42/Aβ40) are measured at baseline, 6, 12 months.

Cognitive outcomes (CDR-SB, ADAS-cog, ADAS-ADL, IADRS Clinical Impression of Change, MMSE) are assessed at baseline, and weeks 12, 24, 40, 52.

- Dose escalation is adjudicated by a Data Safety Monitoring Board (DSMB) that examines safety data and recommends continuation of current dosing and escalation to the next dose or dose modification.

PRECISE-AD Trial Design

12-month Double-blinded Treatment, N=100 Completers
Interim analysis of blinded 6-month biomarker data



Pharmacodynamic engagement: Assess pharmacodynamic markers of treatment effect at baseline, 3, 6, 9, 12 months; Sufficient power to detect biomarker changes at 6 months[3,4].

ARIA: Provides 95% confidence to detect at least one ARIA case.

Plasma Biomarkers: 0, 3, 6, 9, 12 months

CSF Biomarkers: 0, 6,12 months

MRI for ARIA at baseline and weeks: 6,14,24,30,38,46, 52

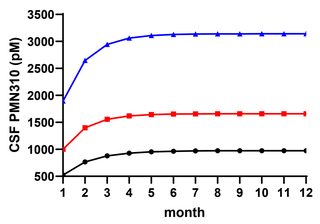
Aβ PET: baseline, month 12

Clinical endpoints (cognition) measured at baseline and weeks : 12, 24, 40, 52

- CDR-SB
- ADAS-cog
- ADAS-ADL
- IADRS
- Clinical Global Impression of Change
- MMSE

- MRI T2-weighted fluid-attenuated inversion recovery (T2/FLAIR) sequence to detect ARIA-E. Diffusion–weighted imaging (DWI) for ARIA-E clarification.
- MRI gradient recalled echo (GRE) sequence to detect ARIA-H.
- Global and regional brain volumes and regional cortical thickness will be derived from the volumetric MRI sequence (3DT1).
- Task-free functional MRI imaging and diffusion tensor imaging (DTI).

PMN310 expected to saturate AβO at all doses

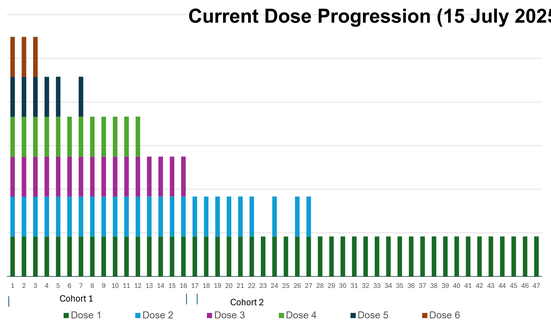


CSF concentration of AβO approximately 1 -10 pM

ca. 50 -300 to 500-3000 x molar excess of PMN310 to AβO across dose range at all doses

Simulated Multiple Dose CSF concentration of PMN310

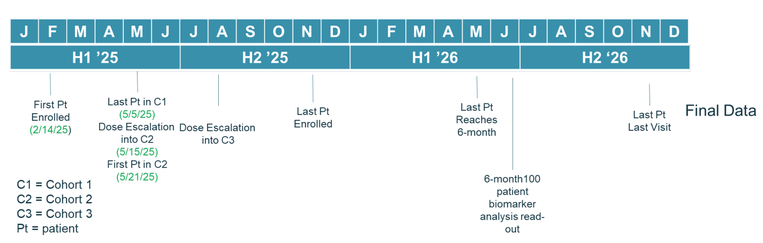
Current Dose Progression (15 July 2025)



Safety to Date (15 July 2025)

- To date *no* ARIA findings in 47 patients who have received at least one dose of PMN310.
- One SAE in a patient who was hospitalized post screening LP. The patient did not randomize or dose. Considered to be unrelated.

Precise-AD Timeline



Results

1. The study has >95% power to detect at least one ARIA event.
2. ***No ARIA observed to date,*** 47 patients dosed.
3. No drug-related SAE to date.
4. Target saturation expected at all doses.
5. Enrollment on proposed timeline.
6. The proposed sample size has sufficient power to provide statistically meaningful insight into effects of PMN310 on biomarkers and clinical outcomes.[3,4]

Conclusion

PRECISE-AD will be the first study to examine the effects of a monoclonal antibody directed solely against AβO on biomarkers associated with AD pathology, safety, and clinical outcomes.

References

1. Gibbs E, Silverman JM, Zhao B, et al. A Rationally Designed Humanized Antibody Selective for Amyloid Beta Oligomers in Alzheimer's Disease. *Sci Rep*. 2019;9(1):9870. Published 2019 Jul 8. doi:10.1038/s41598-019-46306-5.
2. Kaplan JM, Gibbs E, Coutts J, Zhao B, Mackenzie I, Cashman NR. Relationship Between Therapeutic Activity and Preferential Targeting of Toxic Soluble Aggregates by Amyloid-Beta-Directed Antibodies. *bioRxiv*. Published online July 29, 2024. doi:10.1101/2024.04.20.590412.
3. Duncan G, Dickson S, Kaplan J, Johnson S, Duke T, Dayley C, Hendrix S, Altstiel L Mallinckrodt C. Leveraging recent advances in biomarkers to optimize early phase drug development in Alzheimer's Disease. (submitted to *Alzheimer's & Dementia*, 2025.
4. AAIC 2025 Poster #103841 *Monday, July 28, 2025:* Leveraging Recent Advances in Plasma Biomarkers to Optimize Early Phase Drug Development in Alzheimer's Disease. Garrett B. Duncan[1], Suzanne B. Hendrix[1], Samuel P. Dickson[1], Johanne M. Kaplan[2], Tyler M. Duke[1], Samuel B. Johnson[1], Caleb W. Dayley[1], Larry D. Altstiel [2], Craig H. Mallinckrodt[1]
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