Phase 1a Single Ascending Dose Study of PMN310, a monoclonal antibody directed against toxic Aβ oligomers

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Clinical Trial Registry: NCT06105528 https://clinicaltrials.gov

Background

Toxic oligomers of misfolded Aβ peptide (AβO) are implicated in the progression of Alzheimer's disease (AD) [1]. PMN310 is a humanized IgG1 monoclonal antibody that binds to a computationally derived three-dimensional epitope (HHQK) specific to misfolded Aβ in AβO. The epitope is absent in native Aβ and inaccessible to antibody in Aβ plaque [2]. PMN310 does not bind to Aβ plaque, binding to AβO is not significantly inhibited by Aβ monomer, and PMN310 preserves memory in mouse models of AD [3]. Because PMN310 can potentially inhibit the toxicity of AβO and does not bind to plaque, thereby possibly limiting the risk of amyloid-related imaging abnormalities (ARIA), it is being developed as a therapy for early AD.

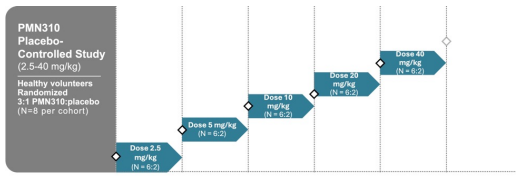
Methods

- This first-in-human study was designed to assess the safety, tolerability, and pharmacokinetics of a single dose infusion of PMN310 in healthy volunteers and guide dose selection for a multiple dose study of PMN310 in early AD patients.
- The study was a double-blind single ascending dose study in 40 healthy volunteers. Men and women, age 18-65, who had no medical conditions that precluded safe participation in the study were eligible. After providing informed consent and ascertainment of eligibility, patients were randomized to either active PMN310 or placebo in dosing cohorts containing 6 subjects receiving a single intravenous infusion of PMN310 and 2 subjects receiving saline placebo infusion.
- There were five dosing cohorts: 175 mg, 350 mg, 700 mg, 1400 mg, 2800 mg.
- The decision to escalate dosing was made by a data safety monitoring board based on safety.
- Serum PMN310 concentrations were collected before, and at the end of the infusion and at 0.5, 1, 2, 4, 8, 12, 24, 36, 72 ,192 hours and approximately biweekly after infusion.
- CSF collection was done at day 3 and day 29 after dosing to determine CSF concentration of PMN310. Routine laboratory, and safety assessments were done at screening, before infusion, and periodically post infusion. Anti-drug antibody samples were collected at baseline and on days 29, 57, and 85.

Results

- There were no adverse events that precluded dose escalation. Across the entire dosing range, plasma concentrations of PMN310 were linearly dose proportional as were total exposure ($AUC_{0-\infty}$) and maximum concentration (C_{max}).
- CSF concentrations of PMN310 were linearly dose-dependent and 100-600 times the estimated CSF AβO molar concentration. The plasma half-life ($t_{½}$) was approximately 17.5 days and the CSF $t_{½}$ was approximately 27 days.
- The estimated binding constant of PMN310-AβO binding is 0.5 nM, suggesting that the 350 mg dose can provide greater than 50% antibody saturation.
- Low-titer anti-drug antibody levels occurred in 3 subjects

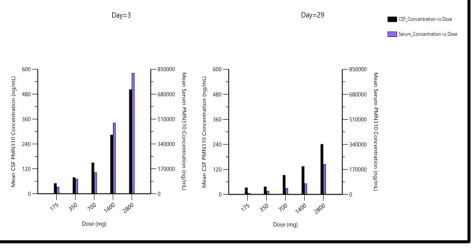
PMN310 Phase 1a Study Design



Subject Demographics

Average Age	Race	Sex
42.1 ± 9.5 years	65% White; 35% Black	77.5% Male; 22.5% Female

Mean Plot of CSF *vs* Serum PMN310 Concentrations by Dose



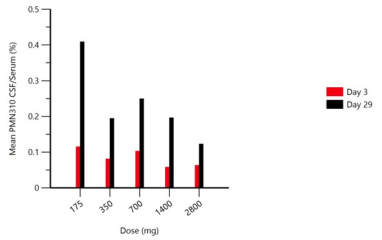
PMN310 was well tolerated

Adverse Event	Outcome	Serious event	Relationship to PMN310 treatment
LEUKOPENIA	Recovered/Resolved	No	Possible
NEUTROPENIA	Recovered/Resolved	No	Possible
NEUTROPENIA	Recovered/Resolved	No	Possible
UPPER RESPIRATORY INFECTION	Recovered/Resolved	No	Possible
VASOVAGAL REACTION	Recovered/Resolved	No	Unlikely
INSOMNIA	Recovered/Resolved	No	Unlikely
UPPER RESPIRATORY INFECTION	Recovered/Resolved	No	Possible
VASOVAGAL REACTION	Recovered/Resolved	No	
ELEVATED CPK DUE TO PHYSICAL EXERTION	Recovered/Resolved	No	Unlikely
VASOVAGAL REACTION	Recovered/Resolved	No	Unlikely
VASOVAGAL REACTION	Recovered/Resolved	No	Unlikely
VASOVAGAL EPISODE	Recovered/Resolved	No	Unlikely
HEADACHE OCCIPITAL	Recovered/Resolved	No	Unlikely
HEADACHE OCCIPITAL	Recovered/Resolved	No	Unlikely
RIGHT WRIST FRACTURE	Recovered/Resolved	No	Unlikely
RIGHT WRIST FRACTURE SURGERY	Recovered/Resolved	No	Unlikely
LOW eGFR	Recovered/Resolved	No	Possible
HYPERSENSIVITY SKIN REACTION (ECG ELECTRODE ADHESIVE REACTION)	Recovered/Resolved	No	Unlikely

Summary

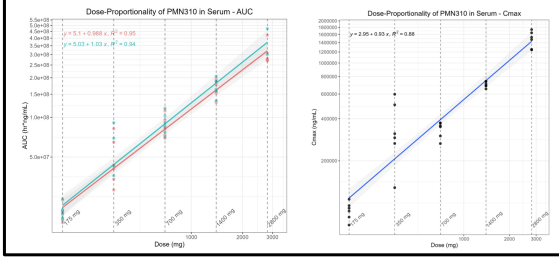
- 18 AE in 15 unique subjects
- 6 AE possibly related, 12 unlikely related per investigator
- No SAE
- No AE precluded dose escalation
- Subject with neutropenia had history of pre-existing neutropenia

Mean Percentage of PMN310 CSF to Serum Concentration

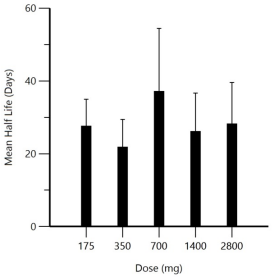


Linear serum PMN310 dose proportionality for AUC and C_{max}

Serum PMN310 dose proportionality was analyzed using the power model: $\ln PK = \alpha + \beta * \ln(dose)$; where PK represents the PK parameter AUCs and C_{max}.



PMN310 half-life in CSF

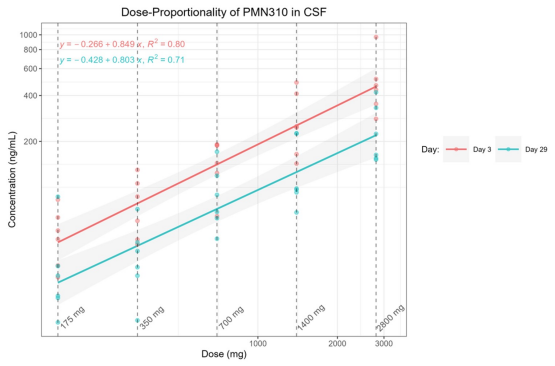


Mean CSF PMN310 half-life ($t_{1/2}$) was estimated roughly using the following formula:

$t_{1/2} = \ln 2 / K_{el}$,

where $K_{el} = \ln(C_{max}/C_{min})/\Delta t$, *and* C_{max} *and* C_{min} *are maximum and minimum CSF concentrations of PMN310 and* Δt *= time interval.*

Linear dose proportionality of PMN310 in CSF



Conclusions

- Data from this study indicate that monthly dosing will provide levels of PMN310 adequate for target engagement.
- The data allowed us to establish dosing schedule and dosing levels for a 100 patient, 12-month study of PMN310 in MCI due to AD and mild AD. The trial is designed to assess safety, ARIA incidence, biomarker activity, and cognitive outcomes.

References

1. *Cline, EN et al. J Alzheimers Dis. 2018; 64 (Suppl 1): S567–S610 doi: 10.3233/JAD-179941.*
2. *Gibbs E. et al. Sci Rep* ***9****, 9870 (2019).* https://doi.org/10.1038/s41598-019-46306-5
3. *Kaplan, JM et al. bioRxiv. 2024.* https://www.biorxiv.org/content/10.1101/2024.04.20.590412v2.