Selective Targeting of Amyloid-β Oligomer Species by PMN310, a Monoclonal Antibody Rationally Designed for Greater Therapeutic Potency in Alzheimer’s Disease

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PHOTO, VIDEO AND AUDIO POLICY

Photography is welcome in this presentation.

Video and audio recording are prohibited.
Soluble Aβ oligomers now recognized as the most neuropathogenic Aβ species -> Spread in a prion-like manner

Specific targeting of toxic Aβ oligomers required for optimal efficacy and safety

# Target Profile for Amyloid-β-Targeted Antibody

<table>
<thead>
<tr>
<th>Property</th>
<th>Therapeutic advantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>No binding to monomers in circulation or CNS</td>
<td>More antibody reaches oligomer target</td>
</tr>
<tr>
<td>No binding to plaque or vascular deposits</td>
<td>Reduced risk of ARIA allows for higher dosing</td>
</tr>
<tr>
<td>Selective binding and neutralization of synthetic toxic oligomers in vitro and in vivo</td>
<td>Therapeutic activity focused on pathogenic target</td>
</tr>
<tr>
<td>IgG4 isotype (low effector isotype)</td>
<td>Reduced risk of inflammation</td>
</tr>
<tr>
<td>High degree of reactivity to toxic oligomer-enriched fraction of AD brain</td>
<td>Effective against native oligomers from patients</td>
</tr>
<tr>
<td>Brain exposure and kinetics equivalent to other antibody candidates</td>
<td>Potential to safely administer high doses with a reduced risk of ARIA likely to result in greater therapeutic potency</td>
</tr>
</tbody>
</table>
COMPUTATIONAL PLATFORM PREDICTS CONFORMATIONAL HHQK EPITOPE OF A\(\beta\) OLIGOMER

Computer modeling identifies sequences (epitopes) likely to be exposed in toxic oligomers but not in monomers or fibrils

\(-\) Regions most prone to exposure thermodynamically

Rationally scaffolded cyclic peptide to mimic the conformation of the epitope as exposed in the oligomer, distinct from the monomer or fibril

\(-\) Use for immunization
PMN310 SELECTIVELY BINDS Aβ OLIGOMERS VS MONOMERS OR PLAQUE

SPR binding response

- huPMN310
- huIgG4

 binding response

hulgG4 isotype control

Vascular deposit

Plaque

Aducanumab

Bapineuzumab

huPMN310

100µm
HIGH PREFERENTIAL BINDING OF PMN310 TO THE TOXIC OLIGOMER-ENRICHED LMW FRACTION OF SOLUBLE AD BRAIN EXTRACT

Reproducible pattern of brain extract fractionation by size exclusion chromatography

High, preferential binding of PMN310 to LMW fraction vs other Aβ-directed antibodies
PMN310 INHIBITS IN VITRO PROPAGATION AND TOXICITY OF Aβ OLIGOMERS

**Inhibition of aggregation propagation in vitro**
(Thioflavin-based assay)

**Inhibition of Aβ oligomer toxicity in vitro**
(Primary mouse cortical neurons)
Administration of PMN310 to mice completely prevents the loss of short-term memory formation caused by toxic oligomers.
Decrease in hippocampal marker of inflammation

Preservation of hippocampal synaptic proteins

**TNF-α**

<table>
<thead>
<tr>
<th></th>
<th>Veh.</th>
<th>PMN310</th>
<th>AβO</th>
<th>PMN310 + AβO</th>
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<tbody>
<tr>
<td>TNF-α</td>
<td>0.1</td>
<td>0.3</td>
<td>0.7</td>
<td>0.5</td>
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**PSD-95**

<table>
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<th>AβO</th>
<th>PMN310 + AβO</th>
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<td>PSD-95</td>
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<td>6</td>
<td>7</td>
<td>6</td>
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**SNAP25**

<table>
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<th>AβO</th>
<th>PMN310 + AβO</th>
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</thead>
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<td>SNAP25</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

* indicates a significant decrease compared to Veh.
# indicates a significant preservation compared to AβO
IN VIVO BRAIN EXPOSURE AND KINETICS

Equivalent CNS penetrance of PMN310 and aducanumab

PMN310 detectable in the brain and circulation out to day 21 post-administration

Human IgG in Brain (ng/g)

Brain
Plasma

Human IgG in Plasma (µg/mL)

PBS
Aducanumab
HuPMN310

Human IgG in Brain (ng/g)

0 100 200 300 400

Human IgG in Plasma (µg/mL)

PBS
Aducanumab
HuPMN310

Human IgG in Brain (ng/g)

0 500 1000 1500

0 100 200 300 400

0 100 200 300 400

0 300 400 500 600

Day 1  Day 7  Day 14  Day 21

24hr
PMN310 may provide greater therapeutic potency and safety compared to other Aβ-directed antibodies

- Selective targeting of toxic Aβ oligomers (not monomers or plaque) should improve oligomer clearance and inhibit disease propagation and neuroinflammation

- Equivalent CNS penetrance and selectivity for toxic Aβ oligomers should translate into a higher effective dose

- Lack of binding to Aβ plaque and vascular deposits, along with an IgG4 isotype, reduces the risk of ARIA and is expected to allow for safe administration of higher doses
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