ProMIS™ Neurosciences

# Elevating Minds, Defeating Dementia

**NASDAQ: PMN**

## Corporate Presentation

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# Pioneering Solutions for Neurodegenerative Diseases

ProMIS uses **Precision Medicine and Artificial Intelligence** to develop **novel drugs** to treat **dementia** and **neurodegenerative diseases**

## Dementia Disorders

- Alzheimer's Disease
- Amyotrophic Lateral Sclerosis (ALS)
- Parkinson's Disease
- Multiple System Atrophy
- Lewy Body Dementia

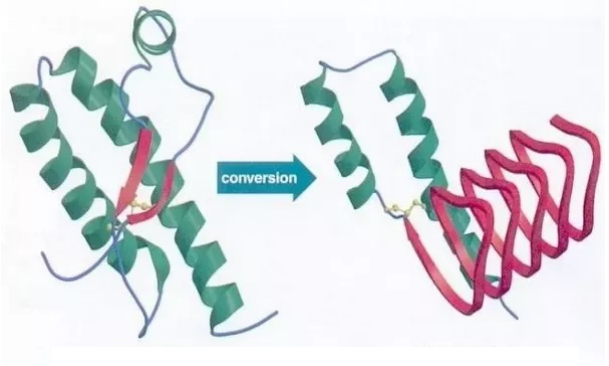
# The Challenge: Impaired Cognition

- According to the World Health Organization, currently more than 55 million people have dementia worldwide
- There are nearly 10 million new cases diagnosed every year[1]
- Dementia is a term for several diseases that affect memory, thinking, and the ability to perform daily activities
- Dementia can lead to death, as it affects the brain and other vital organs
- Dementia is currently the seventh leading cause of death and one of the major causes of disability and dependency among older people, globally
- In the US,  Alzheimer's disease, the most common form of dementia, the Alzheimer's Association reported that over 82,000 people died from Alzheimer's disease in 2019

[1]*WHO Fact sheet*

# Misfolded Proteins: A Leading Cause of Dementia and Neurodegeneration

- Proteins play crucial roles in various cellular functions, and their proper folding is essential for maintaining cellular health.
- However, misfolding, the process in which a protein fails to adopt its correct three-dimensional structure, is a common occurrence.
- Misfolded proteins can arise due to genetic mutations, environmental factors, or errors in cellular processes.
- The gradual and inevitable nature of protein misfolding is part of the aging process
- When proteins misfold, they often lose their functional integrity and may acquire toxic properties.
- Misfolded proteins can aggregate, forming pathogenic clumps that interfere with normal cellular processes.
- These protein aggregates are a hallmark of several neurodegenerative diseases




Normal, healthy protein (folded structure)

Disease associated protein (misfolded)

Aggregation

Toxic

Loss of biological function

Image adapted from Racaniello V et al, virology.ws, 2016

# The ProMIS Solution

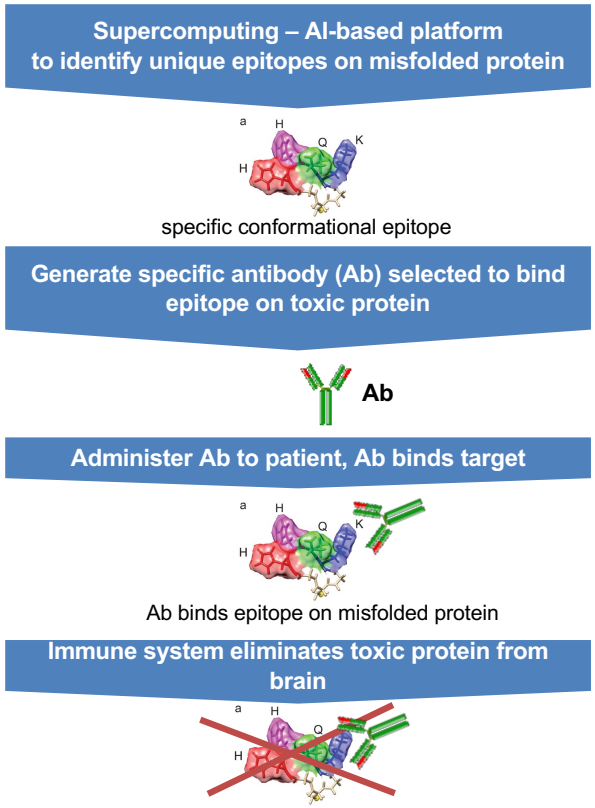
ProMIS has created a Novel, Unique, Patent Protected, Targeted platform to:

1. **Predict disease-specific misfolding of proteins** and identify unique binding sites (epitopes) on each of these misfolded proteins.

2. **Create novel antibodies** that bind strongly only to the specific epitopes allowing the body's immune system to selectively **target and eliminate these toxic proteins** from the brain

3. **Objective: Slow or Halt Disease Progression**

**Misfolded proteins are different for each disease. Therefore, the platform can provide highly specific drug candidates for multiple diseases**



# ProMIS Platform has Generated a Robust Pipeline of Selective Antibody/Vaccine Candidates for Toxic Misfolded Proteins

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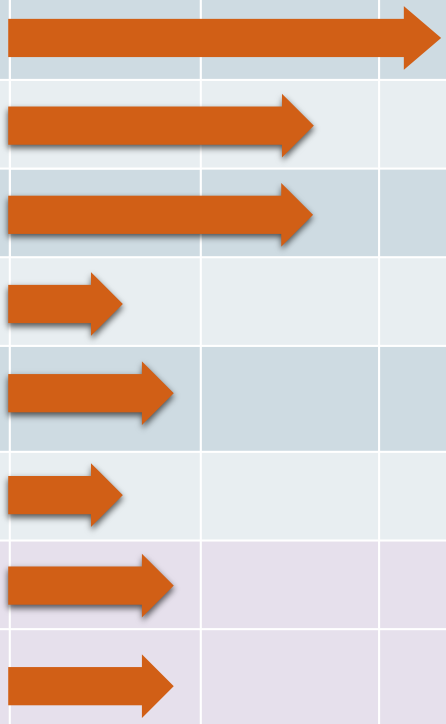
| Product Candidate | Target Protein | Disease Indication | Discovery | Pre-Clinical | Phase 1 | Phase 2 | Phase 3 |
|---|---|---|---|---|---|---|---|
| **PMN310** | Amyloid-Beta | AD | | | | | |
| **PMN267** | TDP-43 | ALS | | | | | |
| **PMN442** | Alpha-Synuclein | MSA[1] | | | | | |
| Discovery | RACK1 | ALS[2], HD | | | | | |
| Discovery | Tau | Alzheimer's[2], FTLD, PSP, CBD | | | | | |
| Discovery | DISC1+Interactome | Schizophrenia | | | | | |
| Discovery | Amyloid-Beta Vaccine | Alzheimer's Prevention | | | | | |
| Discovery | Alpha-Synuclein Vaccine | Synucleinopathies Prevention | | | | | |



*[1] The company plans to investigate additional synucleinopathies, including Parkinson's disease and dementia with Lewy bodies [2]Initial indication*
*AD: Alzheimer's disease, ALS: Amyotrophic lateral sclerosis, MSA: Multiple system atrophy, HD: Huntington's disease, FTLD: Frontotemporal lobar degeneration, PSP: Progressive supranuclear palsy, CBD: Corticobasal degeneration*

# ProMIS Computational Platform and Rational Design Capabilities Enabled the Creation of PMN310

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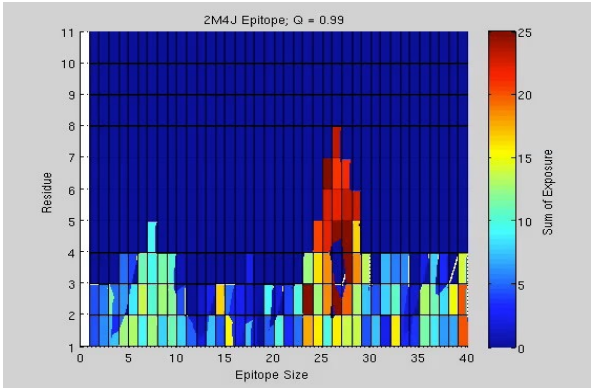
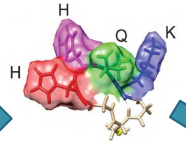
| Computational Modeling | Generation of Monoclonal Antibodies | Selection of Lead Candidate |
|---|---|---|

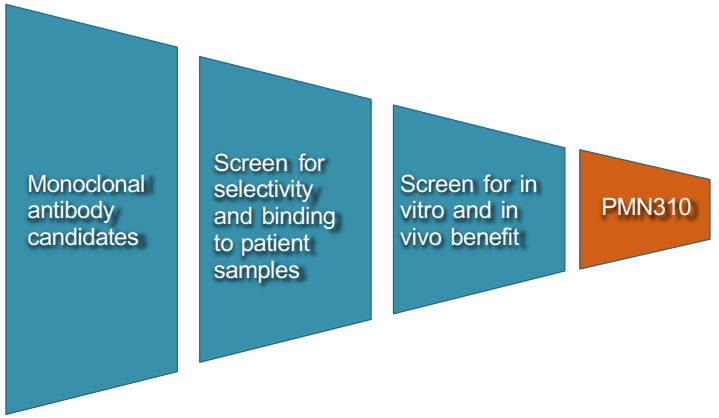



Identification of regions (conformational epitopes) likely to be exposed in misfolded toxic Aβ oligomers but not in monomers or fibrils




Epitope

Immunization with disease-associated conformational epitope




Gibbs et al, 2019, Scientific Reports

**6-8 months to drug candidates**

# ProMIS Extensive Patent Estate

- Over **125 total patent filings** for entire portfolio, growing
- Global patent estate: Applications have been filed in the US, CA, with the EPO, Japan, and other globally strategic regions
- Extensive patent estate for the amyloid area (PMN310 plus other antibodies)
  - 9 issued patents and 43 pending
  - Patent coverage for PMN310 in US until 2036, plus potential data exclusivity extensions to 2042

- **Three-pronged IP strategy**
  1. Composition of Matter: Methods & Systems for Predicting Misfolded Peptide Epitopes (two computational algorithms, ProMIS™ and Collective Coordinates)
  2. Immunogens and methods directed to these disease-specific epitopes
  3. Methods of use: antibodies targeting disease specific epitopes, and methods of use thereof

# Experienced Leadership Team

## Executive Management

**Neil K. Warma**
*Chief Executive Officer*

**Neil Cashman, M.D.**
*Chief Scientific Officer*

**Johanne Kaplan, Ph.D.**
*Chief Development Officer*

**Larry Altstiel, M.D., Ph.D.**
*Chief Medical Officer*

**Gavin Malenfant**
*Chief Operating Officer*

**David Wishart, Ph.D.**
*Chief Physics Officer*

**Dan Geffken**
*Chief Financial Officer*

## Board of Directors

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*Chairman and Co-founder*

**Neil Cashman, M.D.**
*Chief Scientific Officer and Co-founder*

**Neil K. Warma, M.B.A., B.Sc.**
*Chief Executive Officer*

**Maggie Shafmaster, Ph.D., J.D.**
*Lead Independent Director*

**Patrick Kirwin, B.A., J.D.**
*Independent Director*

**Josh Mandel-Brehm, M.B.A.**
*Independent Director*

**William Wyman, M.B.A.**
*Independent Director*

# ALZHEIMER'S DISEASE

# ProMIS Lead Program: PMN310

## Differentiated Antibody Highly Selective for Misfolded, Toxic Oligomers of Amyloid-β

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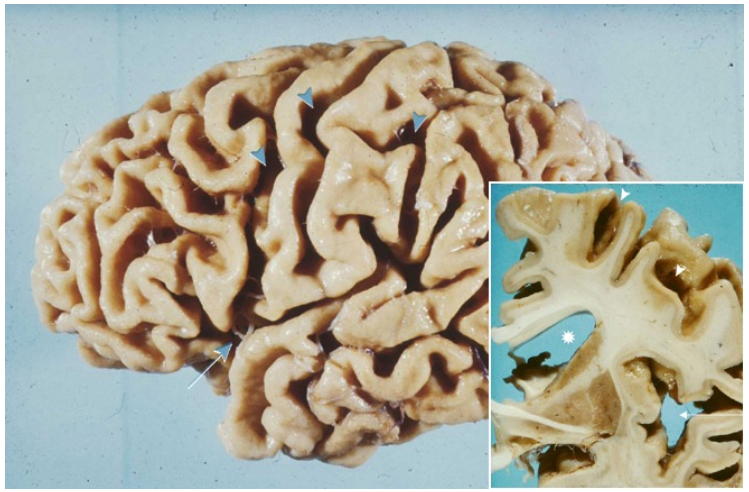
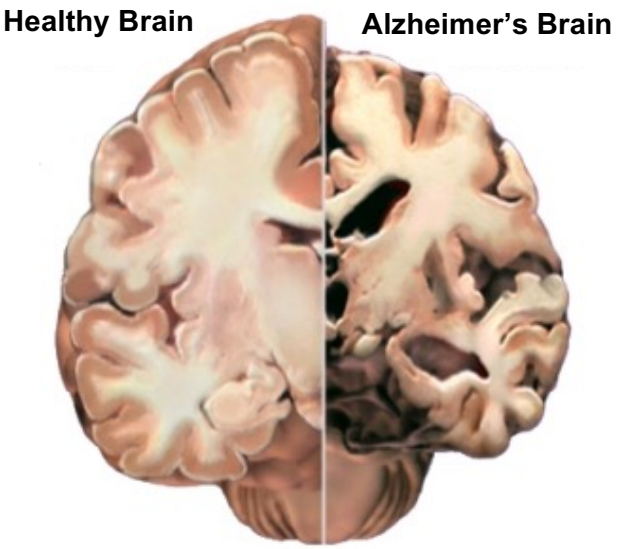
# The Alzheimer's Brain: Neurodegeneration, Atrophy, Dementia






**Anatomic view of the human Alzheimer's brain**

- Evidence of atrophy, or loss of brain substance
- Thinning and widening of brain gyri and fissures
- Enlargements of the fluid spaces, including the lateral ventricle

Images, National Institute on Aging

# Alzheimer's Disease is a Growing Problem: Significant Medical Need, Significant Cost Burden

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## Disease Burden

**9.5 million**
people in the U.S. with mild and progressing cognitive impairment (MCI) or AD

**33%**
prevalence of AD in those over age 85

**4.7 million**
Alzheimer's patients in the U.S. today

**12.7 million**
expected number of Alzheimer's patients in the U.S. by 2050

**6 - 10 years**
average life expectancy after onset of symptoms

## Economic Burden and Opportunity

**$592B**
estimated cost of Alzheimer's

**$321B**
direct medical costs

**$271B**
unpaid family/friend caregiver

**$6.1 Bn**
Est. 2021 global Alzheimer's market

**$13 Bn**
Projected 2021 global Alzheimer's market

**8.1%**
CAGR 2022-2031

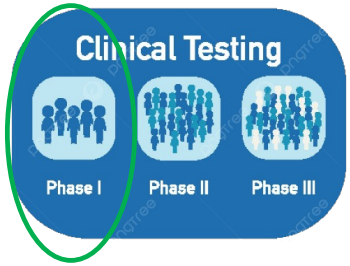
Sources: Alzheimer's Association www.alz.org accessed 25Jan23; direct costs (2022) https://www.alz.org/alzheimers-dementia/facts-figures cost of unpaid caregiving (2021) https://www.alz.org/news/2022/six-essential-alzheimers-terms; Allied Market Research

# PMN310 exclusively targets toxic forms of Aβ oligomers

- Alzheimer's disease (AD) is characterized by the accumulation of misfolded proteins, including **highly toxic amyloid-beta (Aβ) oligomers**
- **Toxic oligomers** are a leading cause of disease pathology in AD
- ProMIS' lead drug candidate (**PMN310**) is a highly specific antibody that **exclusively binds** a specific epitope on the **misfolded Aβ protein in toxic oligomers**
- Binding, we believe, will result in **elimination of the harmful and toxic protein from the brain** to **slow down or halt progression of Alzheimer's**

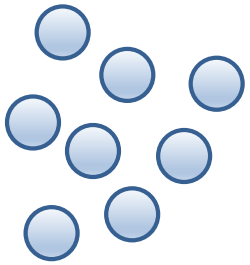
**PMN310 is currently undergoing a Phase 1a human US clinical trial**

**Phase 1a data expected mid-2024**



# Specificity of PMN310 is key to efficacy and safety

## Multiple Forms of amyloid Beta



### Monomers

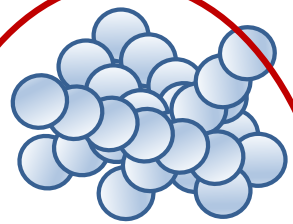
- *Abundant, produced during an entire lifetime*
- *Have a **beneficial** biologic role*

**Most toxic form**

### Oligomers

- *Small and soluble clusters of amyloid beta that can form in the fluid surrounding the nerve cells in the brain*
- ***Highly toxic***
- *Damage the brain cells and cause cognitive decline and dementia*

**PMN310 selectively targets, binds and eliminates only toxic oligomers**

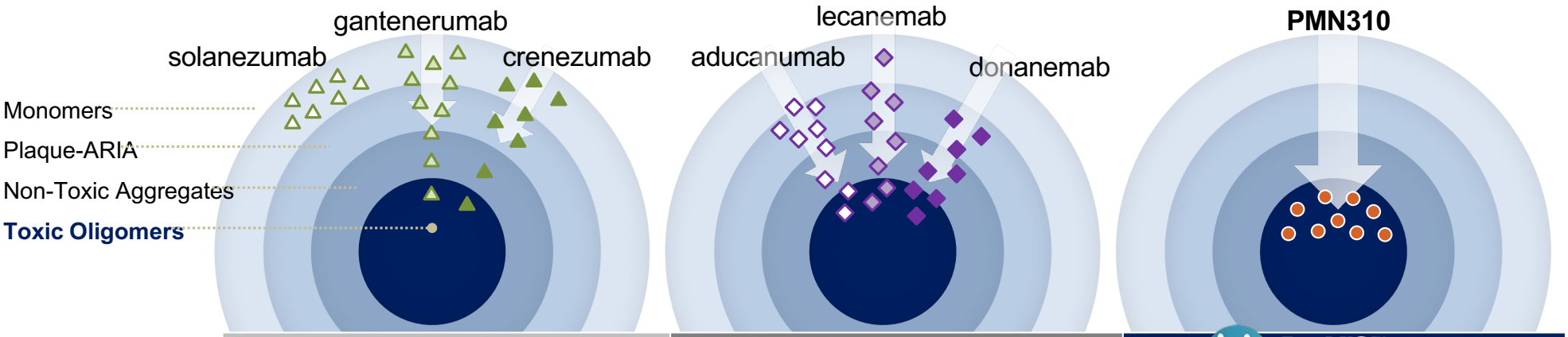


### Plaque

- *Large and insoluble aggregate of amyloid-beta*
- *Forms in the spaces between nerve cells in the brain*
- *Hallmarks of Alzheimer's disease and can cause neuroinflammation*

**Drugs targeting plaque have shown higher incidence of brain swelling and bleeding (ARIA)**

# Differentiation of PMN310 from other Aβ-Directed Antibodies




| | Non-Selective Antibodies | Aggregate-Selective Antibodies | ProMIS™ Neurosciences |
|---|---|---|---|
| Drug | crenezumab, gantenerumab, solanezumab | aducanumab, lecanemab, donanemab | **PMN310** |
| Mechanism | Bind abundant non-toxic monomers/aggregates and are diverted away from the toxic oligomer target | Target oligomers more effectively but incur increased risk of ARIA associated with plaque binding | Specific targeting of toxic oligomers expected to result in increased efficacy and improved safety (reduced risk of ARIA) |
| Clinical Benefit | None | Modest | **Potentially High** |

# PMN310 is differentiated from other Aβ-directed antibodies

| Antibody | Binding to toxic oligomers over monomers | Binding to plaque/ Plaque clearance | ARIA-E | Clinical outcomes |
|---|---|---|---|---|
| PMN310 | +++ | - / TBD | Not Expected | TBD – PMN310 selectivity has potential for greater efficacy (entire dose focused on toxic AβO) and improved safety (no ARIA) |
| PRX h2731 | - | + / TBD | TBD | TBD - Reported "encouraging amyloid reductions" at 6 months |
| ACU193 | +++ | + / + | 21.4% at top dose | Effect on cognition TBD.<br>Improvement in blood and CSF biomarkers. |
| Gantenerumab | - | + / + | ~25% | No cognitive benefit. Some Improvement in blood and CSF biomarkers. |
| Donanemab | ++ | + / + | ~30% | ~29% reduction in cognitive decline (CDR-SB).<br>Improvement in blood and CSF biomarkers. |
| Lecanemab | ++ | + / + | ~15% | ~27% reduction in cognitive decline (CDR-SB).<br>Improvement in blood and CSF biomarkers. |
| Aducanumab | + | + / + | ~35% | ~22% reduction in cognitive decline (CDR-SB).<br>Improvement in blood and CSF biomarkers. |

# PMN310 does not bind plaque, expected to avoid ARIA-E

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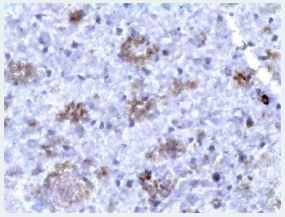
**Plaque-binding antibodies associated with increased risk of ARIA-E[1]**

**Aducanumab**

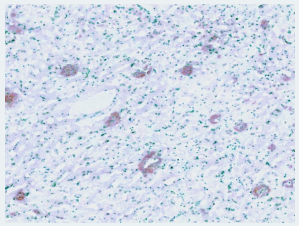
[2]ARIA-E ~35%



**ACU193[6]**

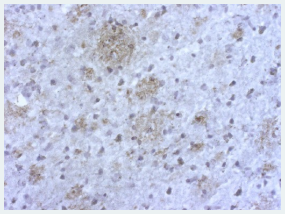
Phase 1- ARIA-E

21.4% at top dose



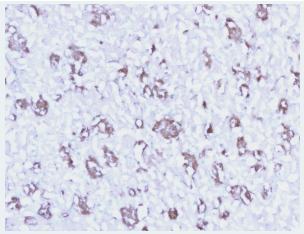
**Donanemab**

[3]ARIA-E ~30%



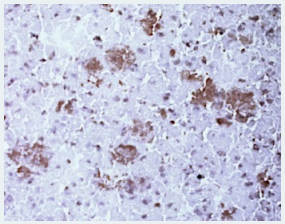
**PRX h2731**

[7]PRX012 Phase 1 ongoing



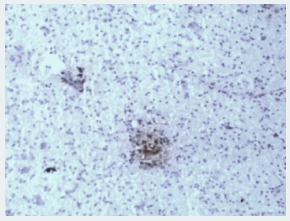
**Lecanemab**

[4]ARIA-E ~15%



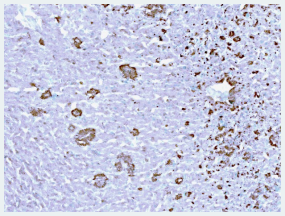
**Crenezumab**

[9]ARIA-E ~0.3%



**Gantenerumab**

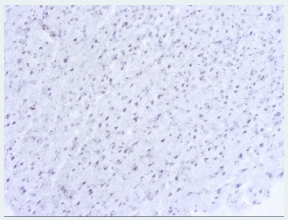
[5]ARIA-E ~25%



**PMN310 shows no detectable plaque binding**

**PMN310**

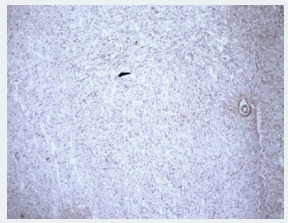
No detectable plaque staining



**Solanezumab**

Minimal plaque binding,

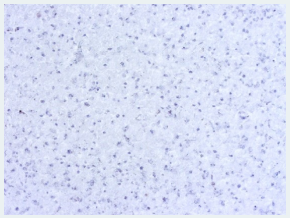
[8]Low incidence of ARIA-E



**huIgG1**

Isotype control

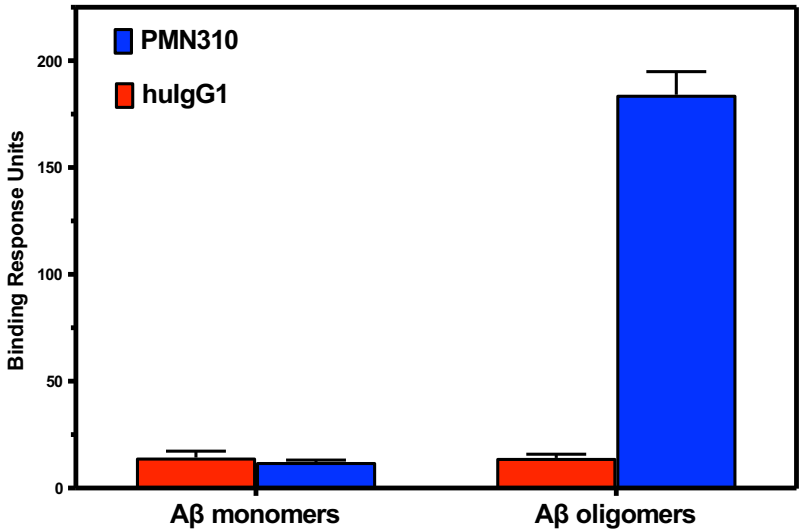
No plaque staining



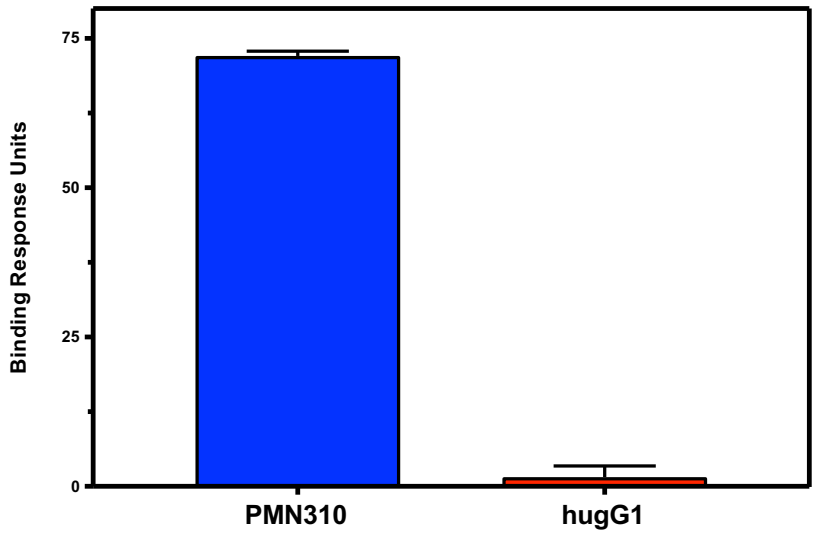
*[1]Sperling RA et al, 2011, Alzheimer's and Dementia; [2]Budd Haeberlein S et al, 2022, J Prev Alz Dis; [3]Mintun MA et al, 2021, NEJM; [4]Swanson CJ et al, 2021, Alzheimer's Research and Therapy; [5]https://www.roche.com/media/releases/med-cor-2022-11-14; [6]Siemers E et al, 2023, J Prev Alz Dis; [7]Tam S et al, 2021, Alzheimer's and Dementia; [8]Ostrowitzki S et al, 2022, JAMA Neurol; [9]Carlson C et al, 2016, Alzheimer's and Dementia*

# PMN310 targets a conformational epitope present on toxic Aβ oligomers, not monomers

**PMN310 selectively binds synthetic Aβ oligomers vs monomers**




**PMN310 shows strong ex vivo target engagement with toxic oligomers in Alzheimer's brain extract**




Surface plasmon resonance (SPR) was used to measure the binding of immobilized PMN310, or a human IgG1 isotype control (huIgG1), to synthetic Aβ monomers or oligomers, and to the toxic oligomer-enriched low molecular weight fraction of soluble AD brain extract (~8-70 kDa)

# PMN310 binding to toxic oligomers is minimally impacted by monomer competition, a potential correlate of clinical efficacy

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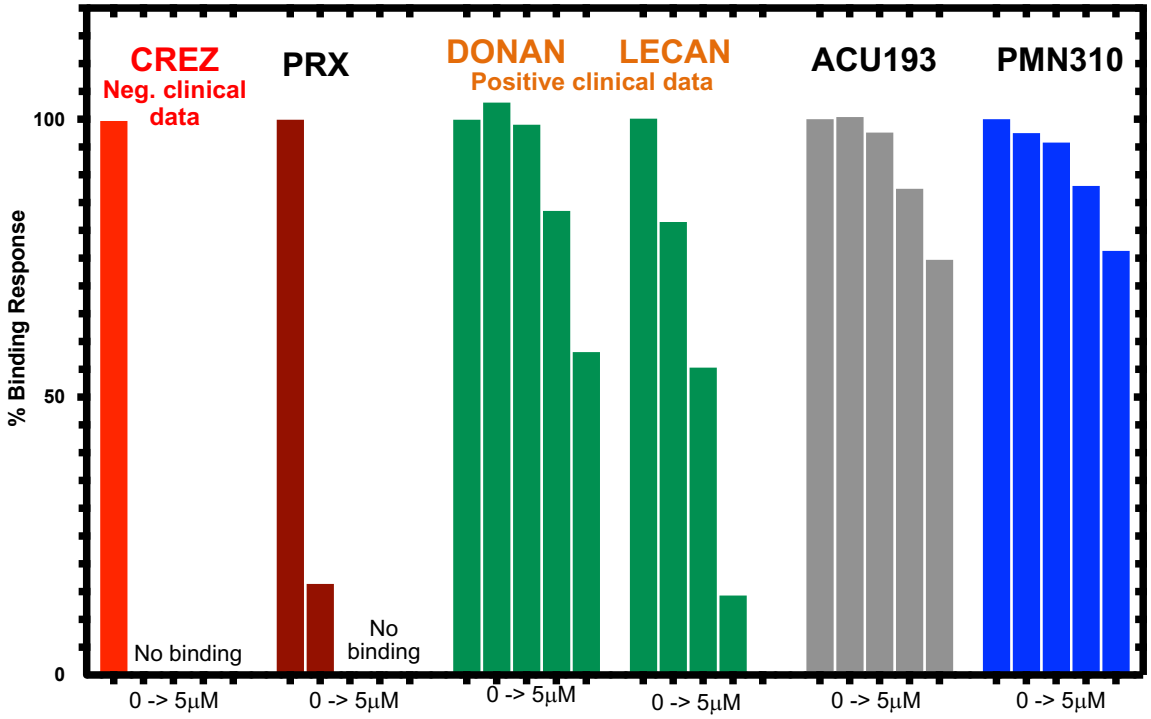
**Binding to toxic oligomer-enriched fraction of AD brain with monomer competition from 0-5 μM**




- Monomer concentrations: 0, 0.08, 0.3, 1.25, 5 μM
- CREZ: crenezumab, PRX: Prothena PRX h2371, DONAN: donanemab, LECAN: lecanemab. All comparator antibodies are biosimilars.
- Percent binding response: [(Binding response units (BRU) with monomers) / (BRU without monomers)]X100

- Antibodies with positive clinical trial data resisted monomer competition, retaining binding to toxic oligomers
- **PMN310 targeting of toxic Aβ oligomers was minimally impacted by monomer competition.** Similar pattern with ACU193
- Antibodies with negative clinical data did not bind toxic oligomers in the face of monomer competition. Also observed with PRX h2731.
- ***In vivo*, plaque binding (not captured in this assay) will result in additional target distraction for all antibodies except PMN310**

Not shown here: solanezumab, gantenerumab sensitive to monomer competition; aducanumab more resistant

# Clinical Differentiation of PMN310

## PNM310 is unique in that it binds only to the toxic oligomer form of amyloid-beta

- PMN310 does not bind plaque or monomers
- Most drugs are not able to distinguish the different forms of Aβ and therefore, bind all three or at least two forms of Aβ
- Drugs that bind several forms of Aβ limit the amount of drug that can bind the key toxic form (oligomers)
- Drugs that bind plaque are associated with increased serious side effects - swelling of the brain (ARIA)

## Expected effect of PMN310

- Higher efficacy (at lower doses)
- Improved safety profile (no ARIA)
- Higher therapeutic index

# ALZHEIMER'S DISEASE

# PMN310 Clinical Development

**Phase 1 study is ongoing in the U.S.**

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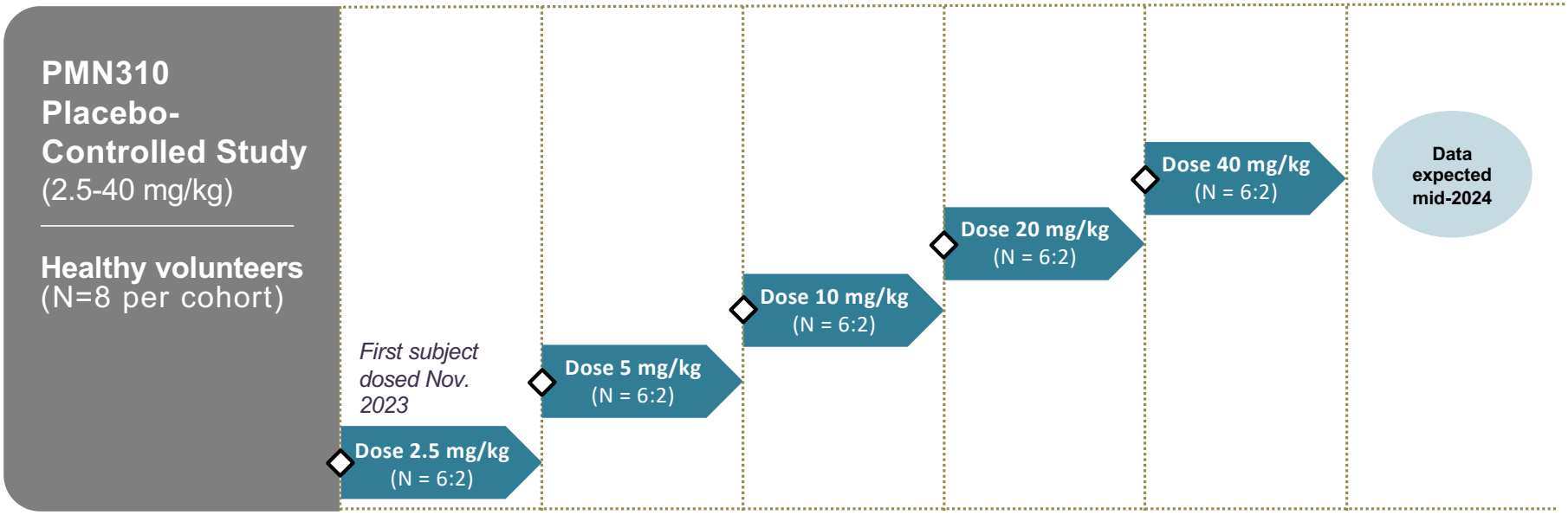
# PMN310 Phase 1a First-in-Human Single Ascending Dose (SAD) PK Study: Ongoing, data expected mid-year

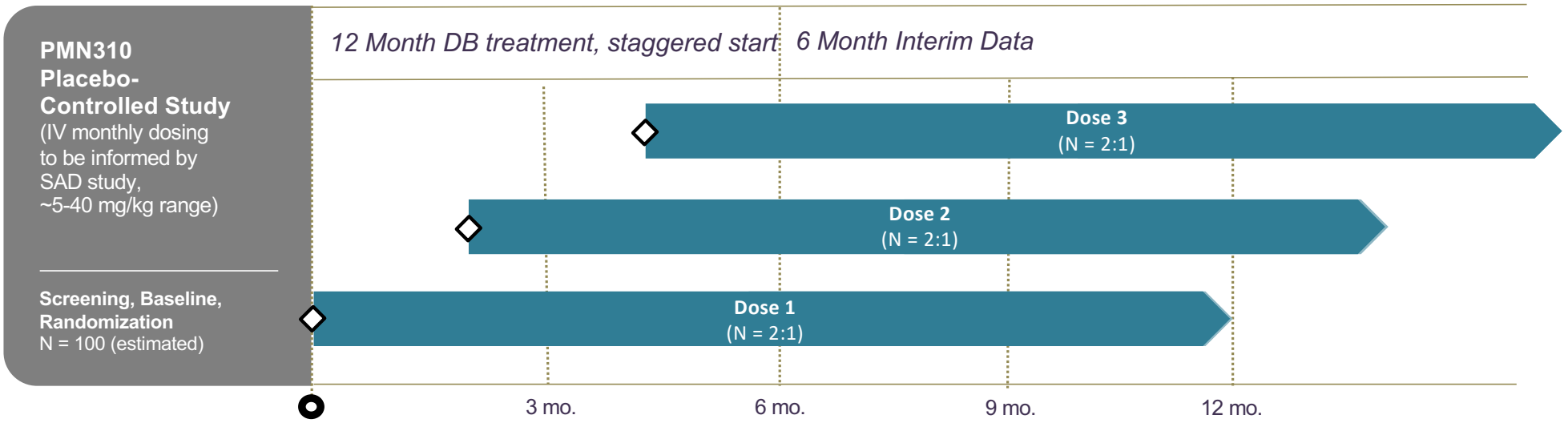



**SAD Study Delivers:**

- Safety and tolerability across wide dose range, enabling confident dose selection for MAD study in AD patients
- Safe, well-tolerated dose that provides CSF concentrations required for target engagement

*SAD, Single Ascending Dose; MAD, Multiple Ascending Dose; AD, Alzheimer's Disease*

# Preliminary PMN310 Phase 1b MAD Trial Design in AD Patients
## 12-month double-blinded treatment, interim 6-month data, N=100 completers




**Efficacy: Assess pharmacodynamic markers of treatment effect at baseline, 3, 6, 9, 12 months**

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

**CSF/ Plasma Biomarkers: 0, 3, 6, 9, 12 month**
- p-tau181, p-tau217, p-tau243
- GFAP
- Neurogranin
- SNAP-25
- Aβ42/40
- NfL

**MRI for ARIA at baseline and months 2, 4, 6, 9, 12**

**Aβ PET**

**Clinical endpoints (cognition) measured at baseline and months 6 & 12:**
- CDR-SB
  (Clinical Dementia Rating, Sum of Boxes)
- ADAS-cog
- ADAS-ADL
- IADRS
- Clinical Global Impression of Change

# ProMIS Investment Thesis

ProMIS™ Neurosciences

# ProMIS Investment Thesis

- Developing novel treatments for multiple dementias and neurodegenerative diseases: strong patent estate
- Unique in its ability to identify novel binding sites (epitopes) on misfolded proteins, responsible for disease progression
- PMN310, lead drug candidate, in the clinic for treatment of Alzheimer's disease
- Phase 1a ongoing, proof of concept 1b trial expected to initiate 2H'24
- PMN310 is unique in ability to only bind the most toxic form of amyloid-beta (toxic oligomers), there appears to be no binding of plaque, and, therefore, fewer side effects, including ARIA (brain swelling/ hemorrhage) are expected
- Broad platform has potential to treat numerous dementias including AD, ALS, Parkinson's, MSA
- Pipeline products are poised to enter clinic with demonstrated Proof-of-Concept in Alzheimer's disease
- World-class management team, global expertise in drug development and commercialization

# Elevating Minds, Defeating Dementia

**NASDAQ: PMN**

For further information, contact:
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