ProMIS™ Neurosciences

Elevating Minds, Defeating Dementia

NASDAQ: PMN

Corporate Presentation

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Pioneering Solutions for Neurodegenerative Diseases

ProMIS™ Neurosciences

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

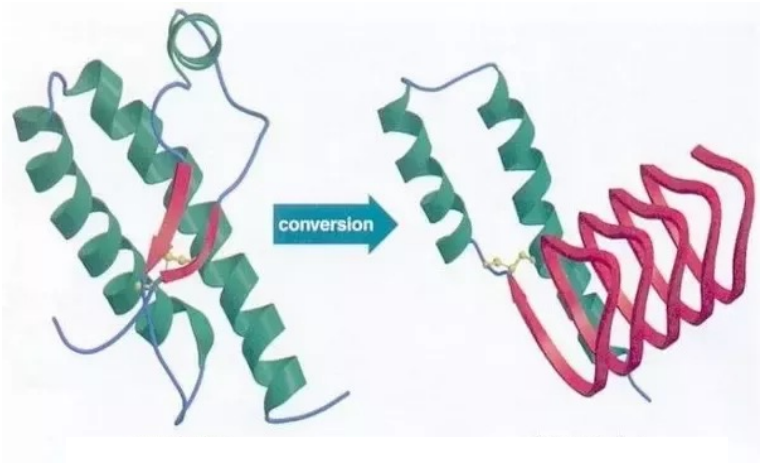
The Challenge: Impaired Cognition

- 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)

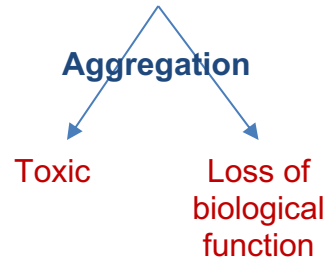


Image adapted from Racaniello V et al, virology.ws, 2016

The ProMIS Solution

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

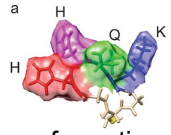
1. **Predict disease-specific misfolding of proteins** and identify unique binding sites (epitopes) on each of these misfolded proteins.

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

Supercomputing – AI-based platform to identify unique epitopes on misfolded protein

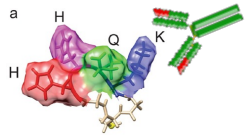


specific conformational epitope

Generate specific antibody (Ab) selected to bind epitope on toxic protein

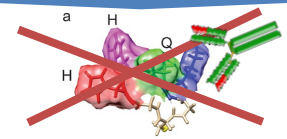
Ab

Administer Ab to patient, Ab binds target



Ab binds epitope on misfolded protein

Immune system eliminates toxic protein from brain



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

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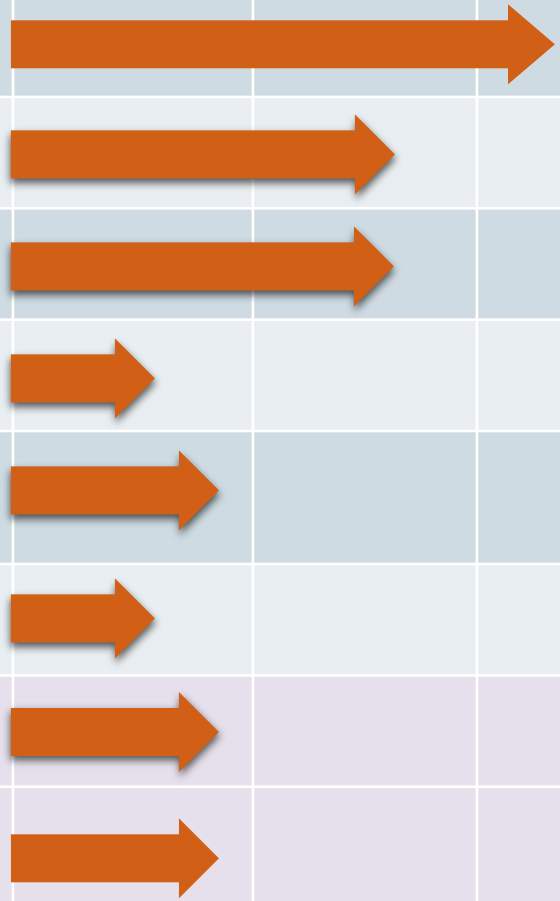
Product Candidate	Target Protein	Disease Indication	Discovery	Pre-Clinical	Phase 1	Phase 2	Phase 3
PMN310	Amyloid-Beta	AD					
PMN267	TDP-43	ALS					
PMN442	Alpha-Synuclein	MSA[1]					
Discovery	RACK1	ALS[2], HD					
Discovery	Tau	Alzheimer's[2], FTLD, PSP, CBD					
Discovery	DISC1+Interactome	Schizophrenia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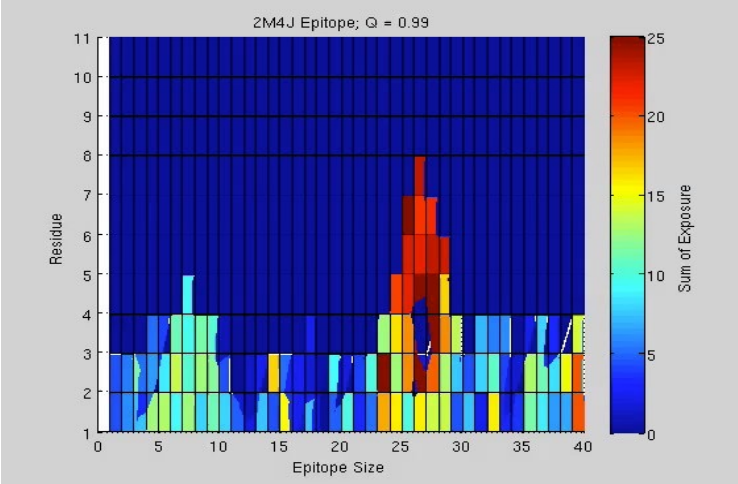
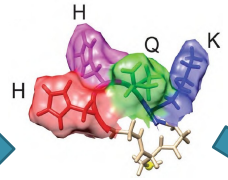
Computational Modeling



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

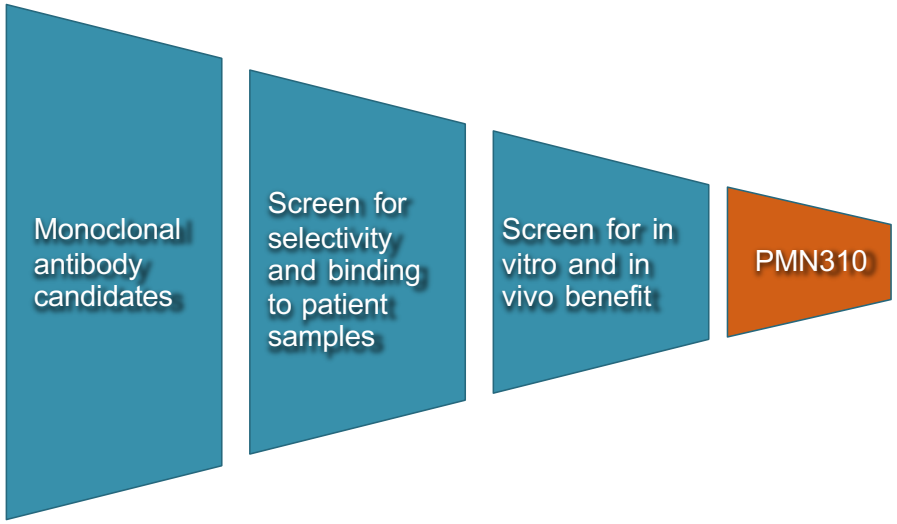
Generation of Monoclonal Antibodies



Epitope

Immunization with disease-associated conformational epitope

Selection of Lead Candidate



Gibbs et al, 2019, Scientific Reports

6-8 months to drug candidates

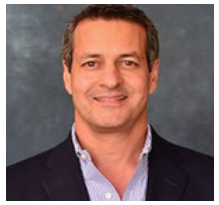
ProMIS Extensive Patent Estate

- 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



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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

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Chief Scientific Officer and Co-founder

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Independent Director

ALZHEIMER'S DISEASE

ProMIS Lead Program: PMN310

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

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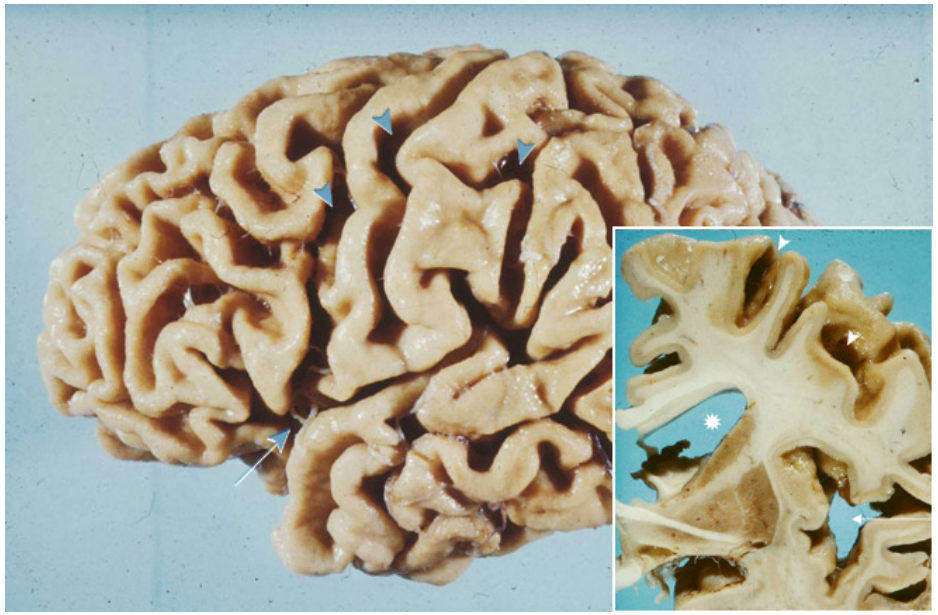
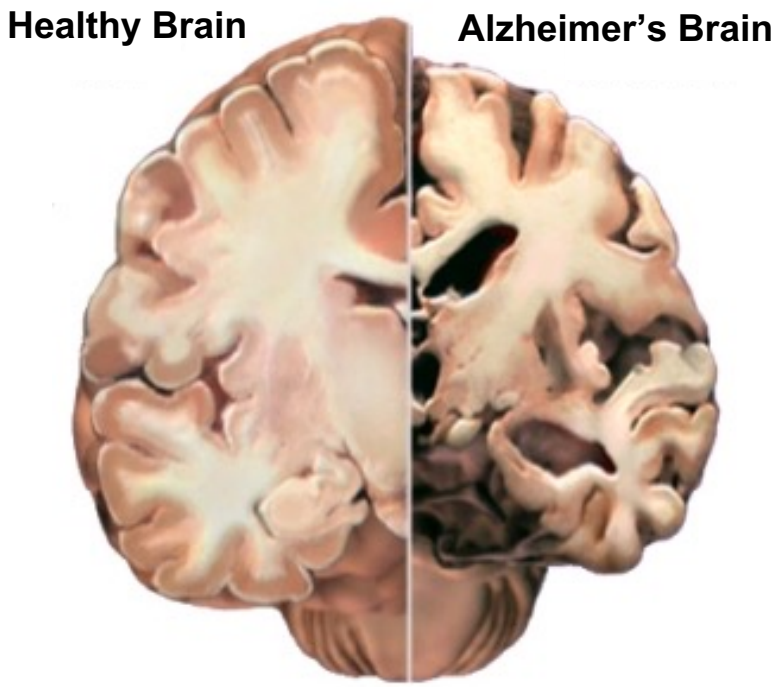
The Alzheimer's Brain: Neurodegeneration, Atrophy, Dementia





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

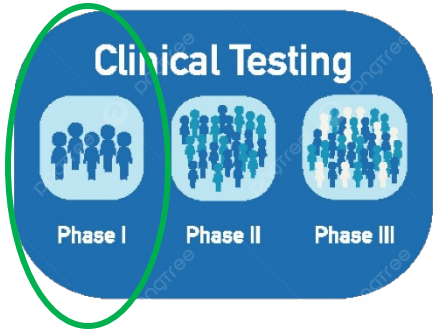
Sources: Alzheimer's Association www.alz.org accessed 25Jan23; direct costs (2022) https://www.alz.org/alzheimers-dementia/facts-figures cost of unpaid caregiving (2021) https://www.alz.org/news/2022/six-essential-alzheimers-terms; Allied Market Research

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**

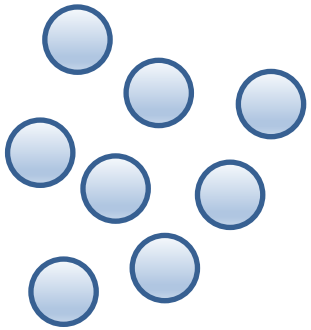
PMN310 is currently undergoing a Phase 1a human US clinical trial

Phase 1a data expected mid-2024



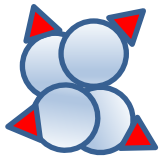
Specificity of PMN310 is key to efficacy and safety

Multiple Forms of amyloid Beta



Monomers

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

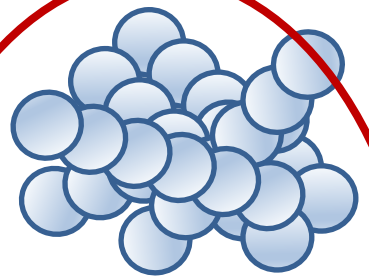


Most toxic form

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

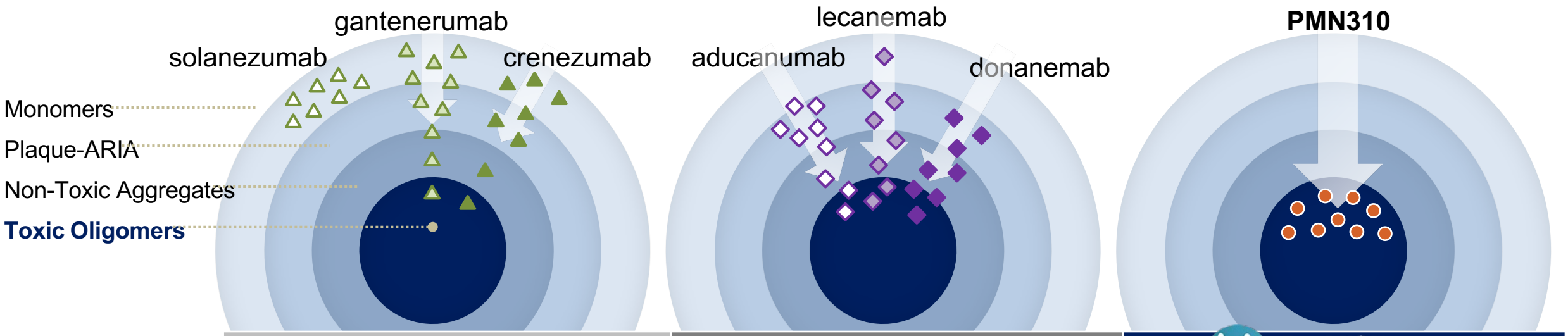


Plaque

- *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 does not bind plaque, expected to avoid ARIA-E

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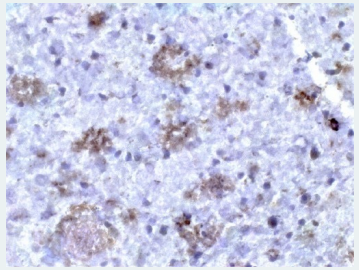
Plaque-binding antibodies associated with increased risk of ARIA-E[1]

Aducanumab

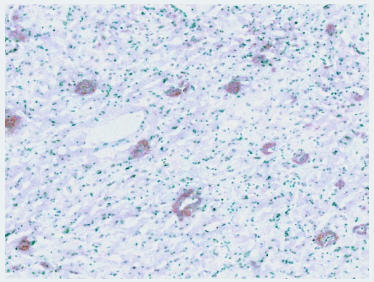
[2]ARIA-E ~35%



ACU193[6]

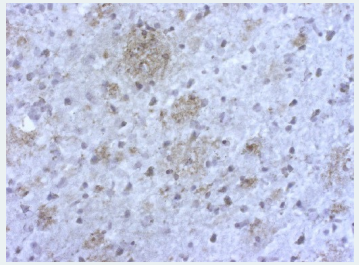
Phase 1- ARIA-E

21.4% at top dose



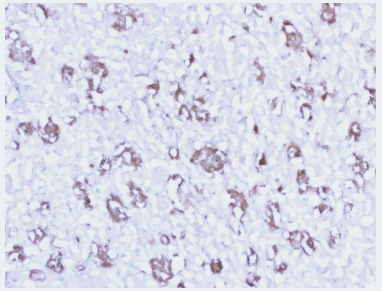
Donanemab

[3]ARIA-E ~30%



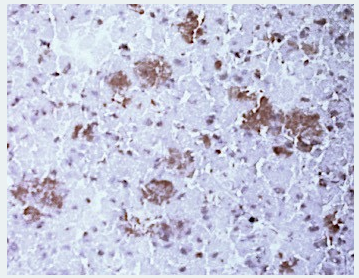
PRX h2731

[7]PRX012 Phase 1 ongoing



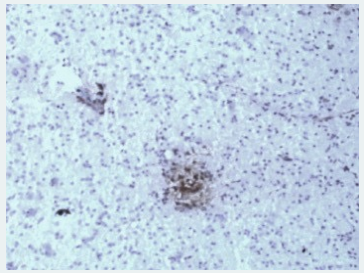
Lecanemab

[4]ARIA-E ~15%



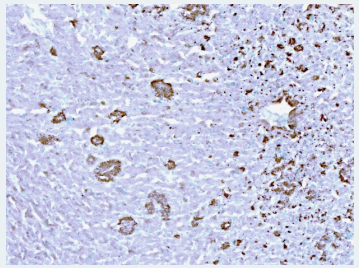
Crenezumab

[9]ARIA-E ~0.3%



Gantenerumab

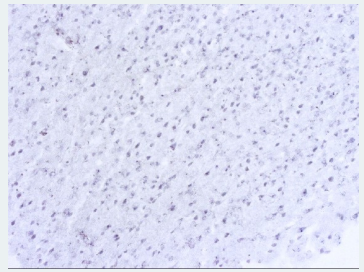
[5]ARIA-E ~25%



PMN310 shows no detectable plaque binding

PMN310

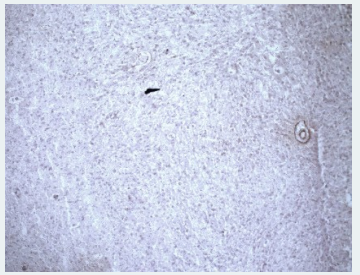
No detectable plaque staining



Solanezumab

Minimal plaque binding,

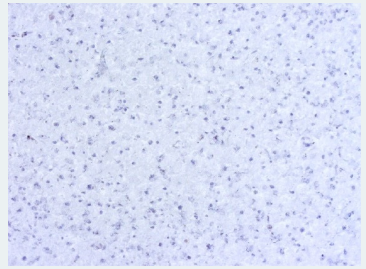
[8]Low incidence of ARIA-E



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

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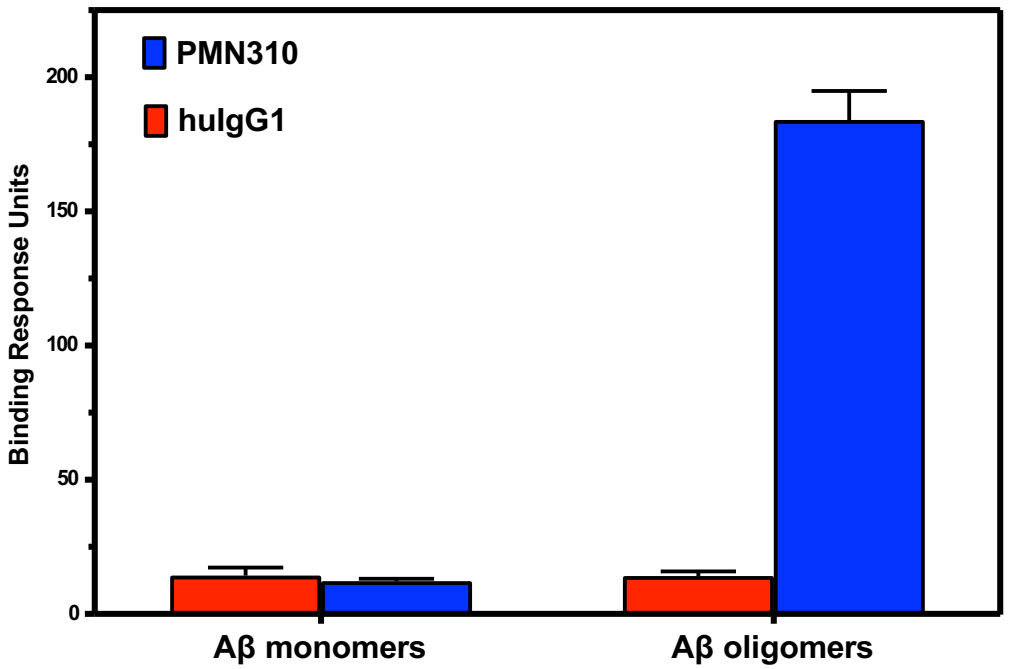
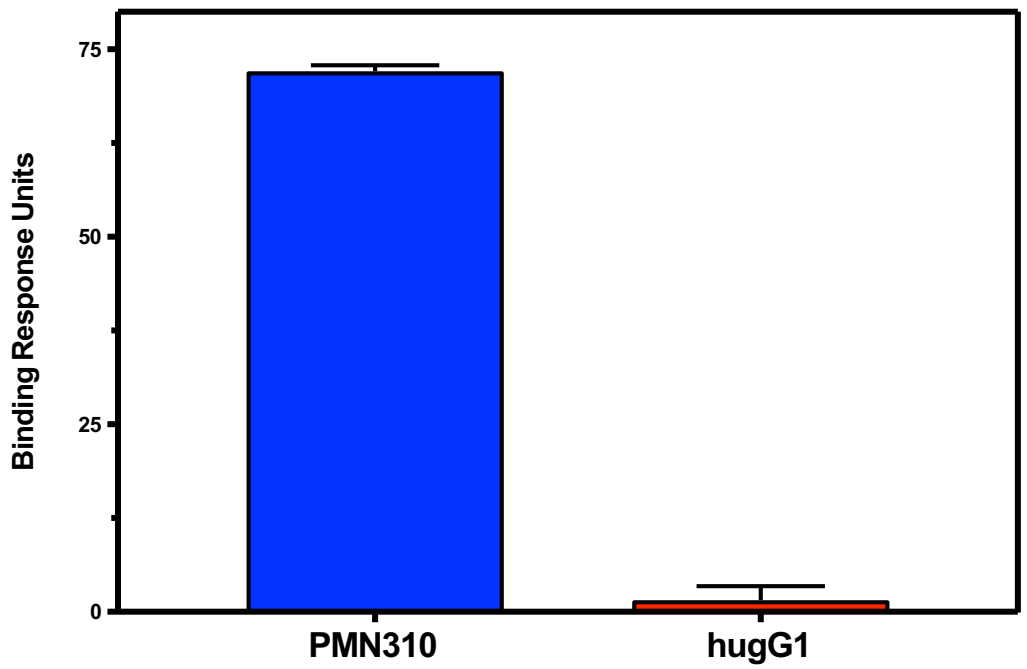
PMN310 selectively binds synthetic Aβ oligomers vs monomers



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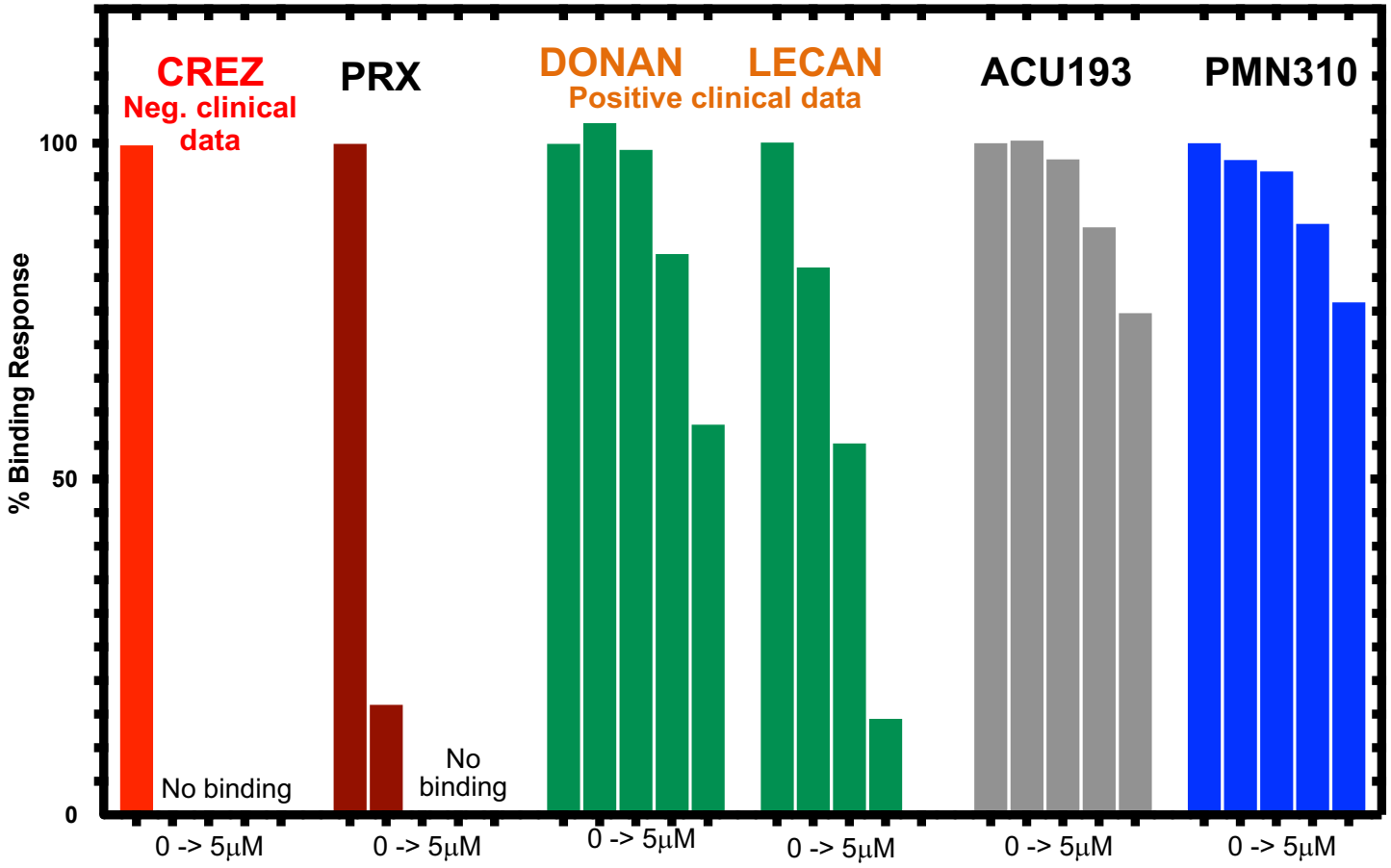
Binding to toxic oligomer-enriched fraction of AD brain with monomer competition from 0-5 □M



- 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**

- Monomer concentrations: 0, 0.08, 0.3, 1.25, 5 □M
- 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

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

Clinical Differentiation of PMN310

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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

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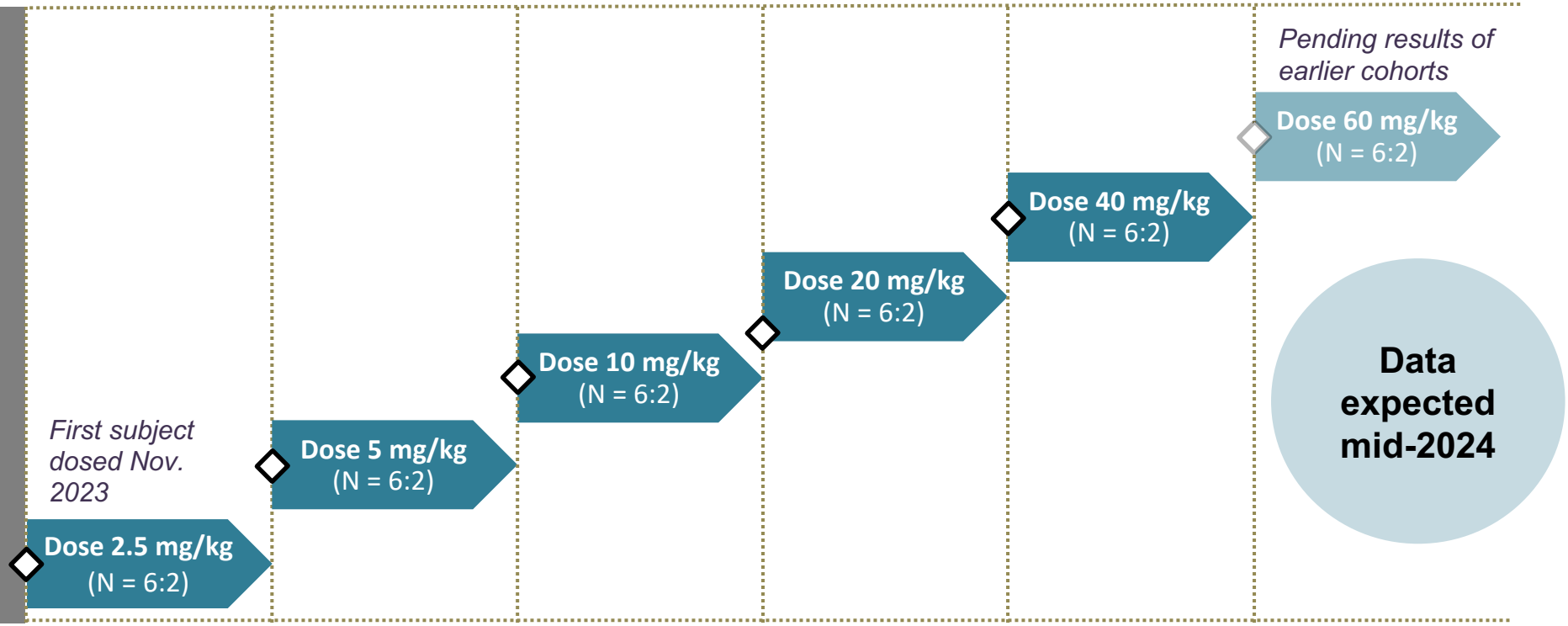
PMN310 Placebo-Controlled Study
(2.5-40 mg/kg)

Healthy volunteers
(N=8 per cohort)

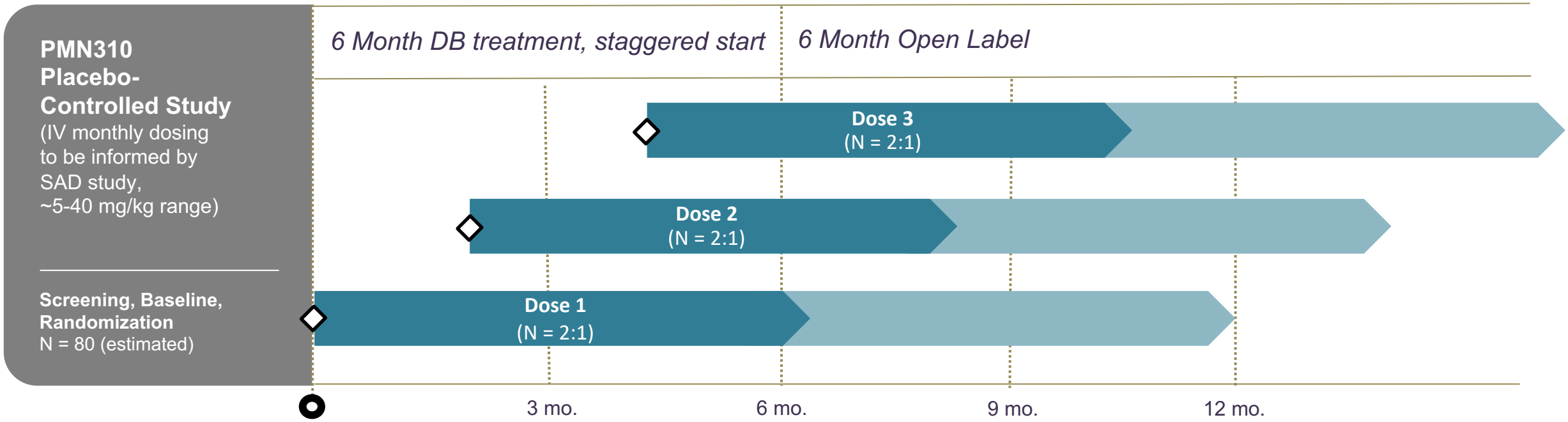


SAD Study Delivers:

- 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

PMN310 Phase 1b MAD Trial Design in AD Patients Assesses Safety (ARIA) and Efficacy (Biomarkers)



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, 5

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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