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Final Results of a Phase 2b Study of Sumifilam in Alzheimer's Disease

September 14, 2020

Forward-Looking Statements & Safe Harbor

This presentation contains “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995. To identify such forward-looking statements, in some cases we use terms such as “predicts, “believes,” “potential,” “estimates,” “anticipates,” “expects,” “plans,” “intends,” “may,” “could,” “might,” “should” or other words that will convey risk or uncertainty of future events or outcomes. All statements other than statements of historical fact contained in this presentation including, but not limited to, statements regarding plans or timing for future Phase 3 clinical studies with sumifilam; the interpretation of prior or current results of our Phase 2 clinical studies, including the measured effects of sumifilam on cognition; plans to publish results in a peer-reviewed journal; potential health benefits, if any, of changes in levels of biomarkers; verbal commentaries made by Cassava Sciences’ employees; and potential benefits, if any, of the Company’s product candidates for Alzheimer’s disease are forward-looking statements.

Such statements are based largely on our current expectations and projections about future events. Such statements speak only as of the date of this presentation and are subject to a number of risks, uncertainties and assumptions, including, but not limited to, those risks relating to the ability to conduct or complete clinical studies on expected timelines, to demonstrate the specificity, safety, efficacy or potential health benefits of our product candidates, the severity and duration of health care precautions given the international outbreak of an infectious disease and including those described in the section entitled “Risk Factors” in our Annual Report on Form 10-K for the year ended December 31, 2019 and future reports to be filed with the SEC.

In light of these risks, uncertainties and assumptions, forward-looking statements and events discussed in this presentation are inherently uncertain and may not occur. Actual results could differ quickly, materially and adversely from those anticipated or implied in the forward-looking statements. Accordingly, you should never rely upon forward-looking statements as predictions of future events.

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The content of this presentation is solely our responsibility and does not necessarily represent the official views of the National Institutes of Health (NIH).

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Company Presenters

Remi Barbier - Chairman, President & CEO

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Nadav Friedmann, PhD, MD - CMO, Board member

Eight FDA drug approvals prior to Cassava Sciences.

Johnson & Johnson Daiichi-Sankyo Abbott

Lindsay H. Burns, PhD - SVP Neuroscience

Abgenix élan UNIVERSITY OF CAMBRIDGE

Eric Schoen - Chief Financial Officer

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Guest Presenter

Dr. Gonzalez-Rojas, MD

Dr. Gonzalez-Rojas is Principal Investigator (PI) on the Phase 2b study of sumifilam, and PI on an ongoing, one-year open-label study of sumifilam in patients with Alzheimer's disease. Dr. Gonzalez-Rojas will be available for commentary during the Q&A session.

Background - Yaneicy Gonzalez-Rojas MD, Internal Medicine, is an ACRP-certified Principal Investigator working in Coral Gables, FL. Besides being an established medical practitioner treating hundreds of Alzheimer's patients annually, she has a keen interest in conducting quality clinical trials. Dr. Gonzalez-Rojas has participated in 13 clinical trials of various investigational drug agents for Alzheimer's disease.

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Our Mission

Cassava Sciences is dedicated to the development of novel approaches to detect and to treat Alzheimer's disease.

Our Company

- Cassava Sciences is dedicated to the development of novel approaches to detect & treat Alzheimer's disease.
- Our initial focus is on developing **sumifilam**, a proprietary, investigational drug to treat Alzheimer's disease.
- Sumifilam is the first of a new class of drugs that target filamin proteins. Filamin-binding molecules are new to Alzheimer's research and may represent an important advance towards the goal of disease-modifying drugs.
- Sumifilam reduces neurodegeneration *and* neuroinflammation in Alzheimer's disease by binding a single target. The underlying science is published in peer-reviewed journals and benefits from long-term scientific and financial support from the National Institutes of Health (NIH).
- In 2019, we announced positive results of an open-label, Phase 2a study of sumifilam in Alzheimer's disease. In 2020, we completed a randomized, placebo-controlled Phase 2b study of sumifilam in Alzheimer's disease, funded by a research grant from the NIH (NIA grant #AG060878). The purpose of this presentation is to inform our stakeholders of the final clinical results of our Phase 2b study with sumifilam in Alzheimer's disease.

Our future goal is to conduct a Phase III efficacy program with sumifilam in Alzheimer's disease.

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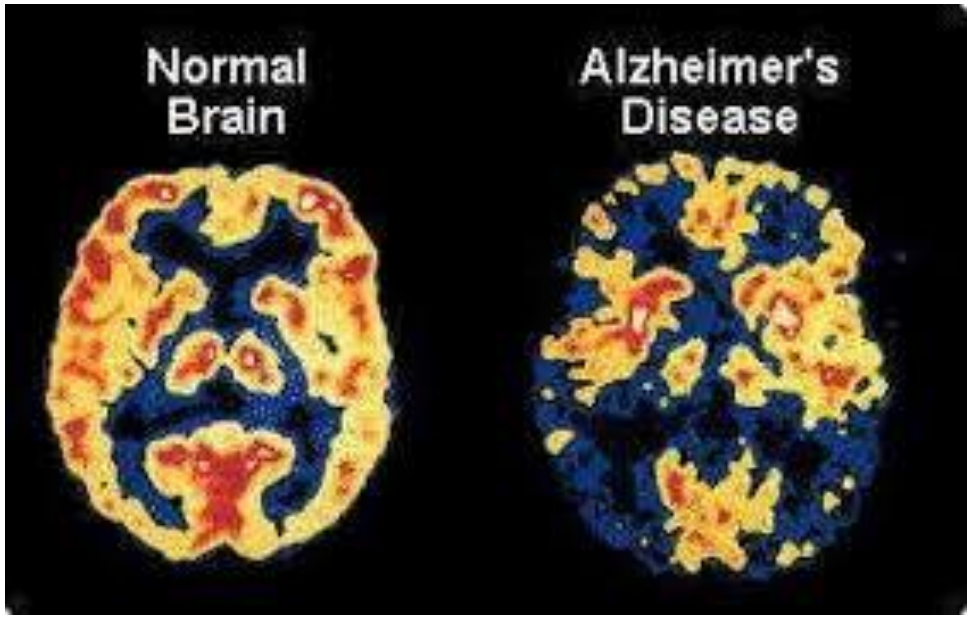
Alzheimer’s Disease – Significant Unmet Needs

- Alzheimer’s disease (AD) is a progressive brain disorder that destroys memory and thinking skills.
- AD is the largest potential drug market in the world, where diagnostic methods are currently limited, treatment options are inadequate and the ability to slow disease progression is non-existent.
- About 5-6 million people live with AD in the U.S. today; incidence is expected to grow dramatically.

There are no disease-modifying therapies for AD patients.



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First Bioanalysis – Invalid Data

As previously reported (May 2020), an outside lab conducted an initial bioanalysis of the Phase 2b study.

Biomarker data received from that lab made no sense. A post-hoc analysis showed significant data anomalies in patients who took placebo for 28 days.

Expected Observations for Patients Who Took Placebo	***Lab's Observations for Patients Who Took Placebo***
Small changes in levels of biomarkers over 28 days. →	*Placebo patients showed large, dramatic swings (>100%) in levels of biomarkers over 28 days.*
Biomarkers generally move in the same direction. →	*Biomarkers appeared to follow a random walk; some moved in opposite directions from each other in the same patient.*
Biomarkers that move in tandem show robust statistical correlations. →	*Changes in levels of biomarkers are uncorrelated (R^2 = 0.06, on average) in placebo patients. See Appendix for more statistical data on placebo patients.*

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Second Bioanalysis – Valid Data

An academic lab conducted a second, final bioanalysis of the Phase 2b study.

The academic lab shows proper biomarker data in patients who took placebo for 28 days.

Data from the academic lab shows modest (4-6%, on average) changes in levels of biomarkers over 28 days; biomarkers that generally move in the same direction; robust statistical correlations ($R^2 = 0.96$, on average) among changes in levels of biomarkers; and negative correlation with Aβ42.

	Aβ42	Total Tau	P-tau181	NfL	Ng	YKL40	IL-6
Aβ42	1	-0.82	-0.89	-0.83	-0.86	-0.82	-0.85
Total Tau	-0.82	1	0.96	0.96	0.97	0.94	0.96
P-tau181	-0.89	0.96	1	0.96	0.97	0.94	0.95
NfL	-0.83	0.96	0.96	1	0.97	0.94	0.97
Ng	-0.86	0.97	0.97	0.97	1	0.92	0.96
YKL40	-0.82	0.94	0.94	0.94	0.92	1	0.96
IL-6	-0.85	0.96	0.95	0.97	0.96	0.96	1

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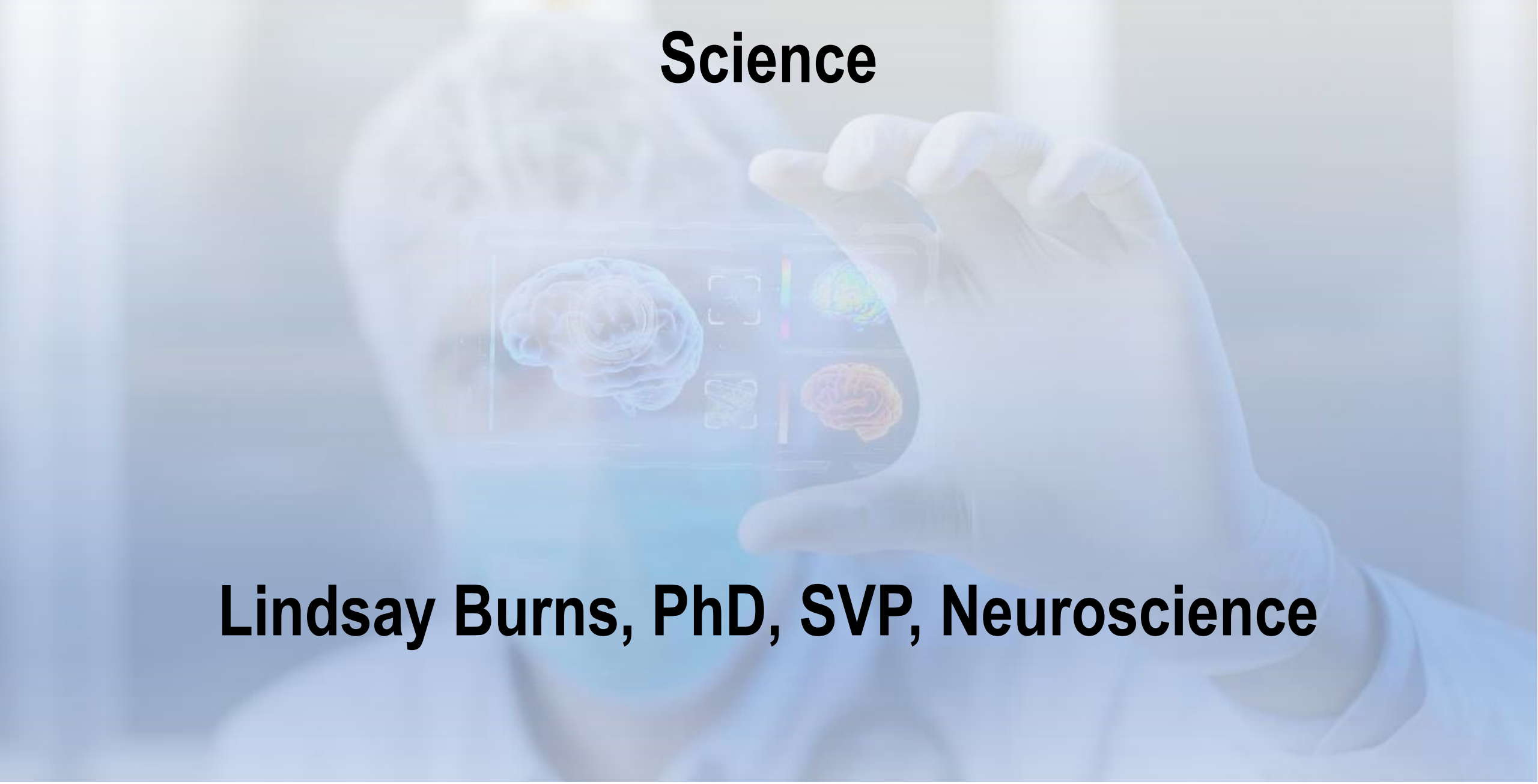
Science



Lindsay Burns, PhD, SVP, Neuroscience

Sumifilam - A Novel Drug for Alzheimer's Disease

- **Sumifilam is our proprietary, small molecule drug candidate to treat Alzheimer's disease (AD) and other dementias and neurodegenerative diseases.**
  - Program benefits from long-term scientific & financial support from the National Institutes of Health (NIH).

- **Sumifilam reduces neurodegeneration *and* neuroinflammation by binding a single target.**

- **In 2020, we concluded a comprehensive Phase 2 clinical testing program of sumifilam in AD, in collaboration with clinical/scientific advisors and NIH.**

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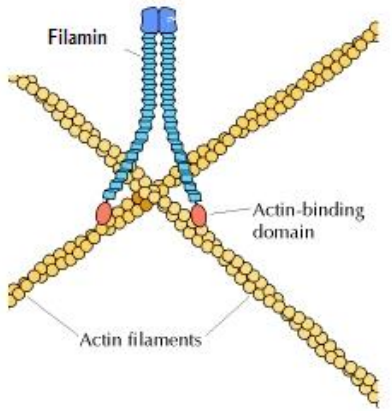
The Target of Sumifilam is *Altered* Filamin A (FLNA)

Filamin A (FLNA) is a scaffolding protein highly expressed in the brain.



FLNA cross-links actin to provide structure and motility, but also interacts with >90 proteins, influencing many signaling pathways.

The Alzheimer's brain carries an *altered* form of FLNA.
Altered FLNA is critical to amyloid beta toxicity.

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Sumifilam Mechanism of Action

- **The altered conformation of FLNA is a proteopathy in the AD brain.**

- **Altered FLNA enables $A\beta_{42}$ signaling via two different receptors:**

  1) **α7-nicotinic acetylcholine receptor (α7nAChR)** → hyperphosphorylates tau
  2) **Toll-like receptor 4 (TLR4)** → releases inflammatory cytokines

- **Sumifilam preferentially binds altered FLNA, restores its proper shape/function, potently suppressing $A\beta_{42}$ signaling via α7nAChR and TLR4.**
  - Through a single target, sumifilam reduces both neurodegeneration & neuroinflammation.

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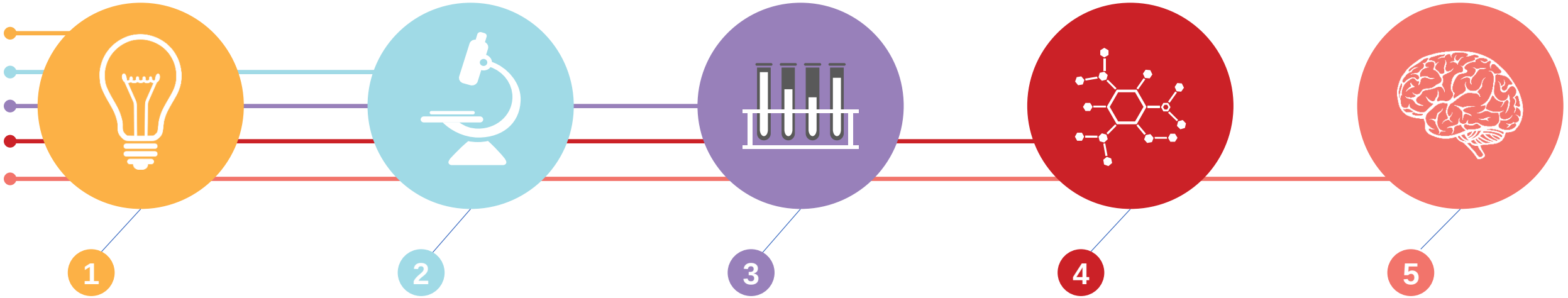
10+ Year Discovery/Development Program



<2008
Basic research around neurobiology of Filamin A (FLNA).

2009
Discovery that altered FLNA associates with α7nAChR when Aβ signals.

2010
Screening/testing of compounds that bind altered FLNA and block α7nAChR/Aβ interaction.

2011
Sumifilam (formerly, PTI-125) binds altered FLNA with high affinity, blocks α7nAChR/Aβ interactions. Preclinical testing of sumifilam.

2017 - present
Clinical testing of sumifilam. Positive results reported in Alzheimer's patients.

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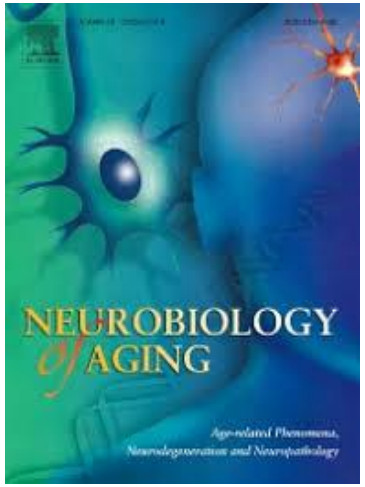
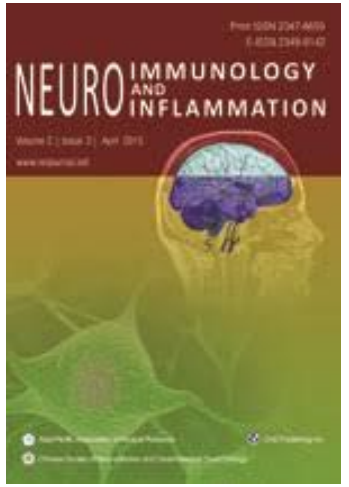
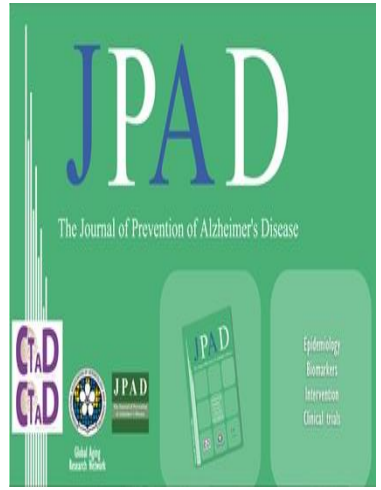
Peer-reviewed Science

The underlying science for sumifilam has been subject to the scrutiny of many experts in the field……







….including NIH, which has awarded our science programs >$10 million in research grant awards.

NIH National Institutes of Health

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Hypothesis and Objective

Clinical Hypothesis

AD patients desperately need disease-modifying drug therapies.

Published pre-clinical data support sumifilam's potential as a disease-modifying drug for AD.

Can sumifilam provide early clinical evidence of disease-modifying effects in a well-controlled study?

Phase 2b Study Objective

Evaluate safety, biomarkers and cognition following 28-day treatment with sumifilam, a new, first-in-class therapy.

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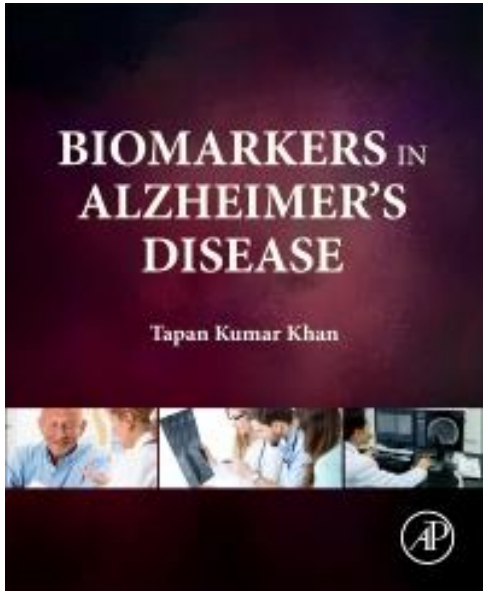
Bring on the Biomarkers



- ***Biological markers ('biomarkers') refers to objective measures of Alzheimer's disease at the level of biology.***
- ***Biomarkers present hard evidence for the presence and progression of Alzheimer's disease.***
- ***Alzheimer's disease can take a decade or more to present. Over that time certain biomarkers rise dramatically, while cognition and health decline.***

One drug, one biomarker is the traditional paradigm in AD research.

Sumifilam's goal is to improve an entire panel of biomarkers of AD pathology, neuroinflammation and neurodegeneration.

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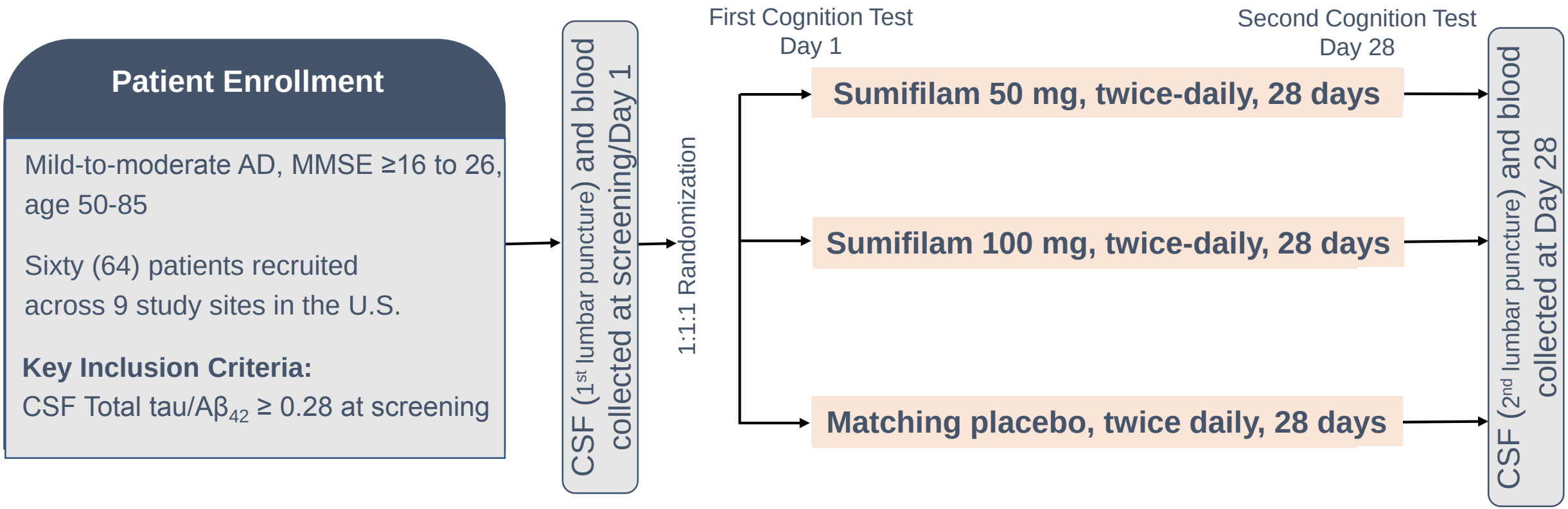
Clinical Results

Nadav Friedmann, PhD/MD, Chief Medical Officer

Lindsay Burns, PhD, SVP, Neuroscience

Phase 2b - Study Design

Randomized, Double-blind, Placebo-controlled, Multicenter Clinical Study



Primary Endpoint: biomarkers of disease

Secondary Endpoint: cognition

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Phase 2b - Safety

- **Sumifilam was safe and well-tolerated**
- **No serious adverse events**
- **No drug-related adverse events**
  - Common, non-persistent side-effects observed in placebo & drug groups
- **No drug-related patient discontinuation**

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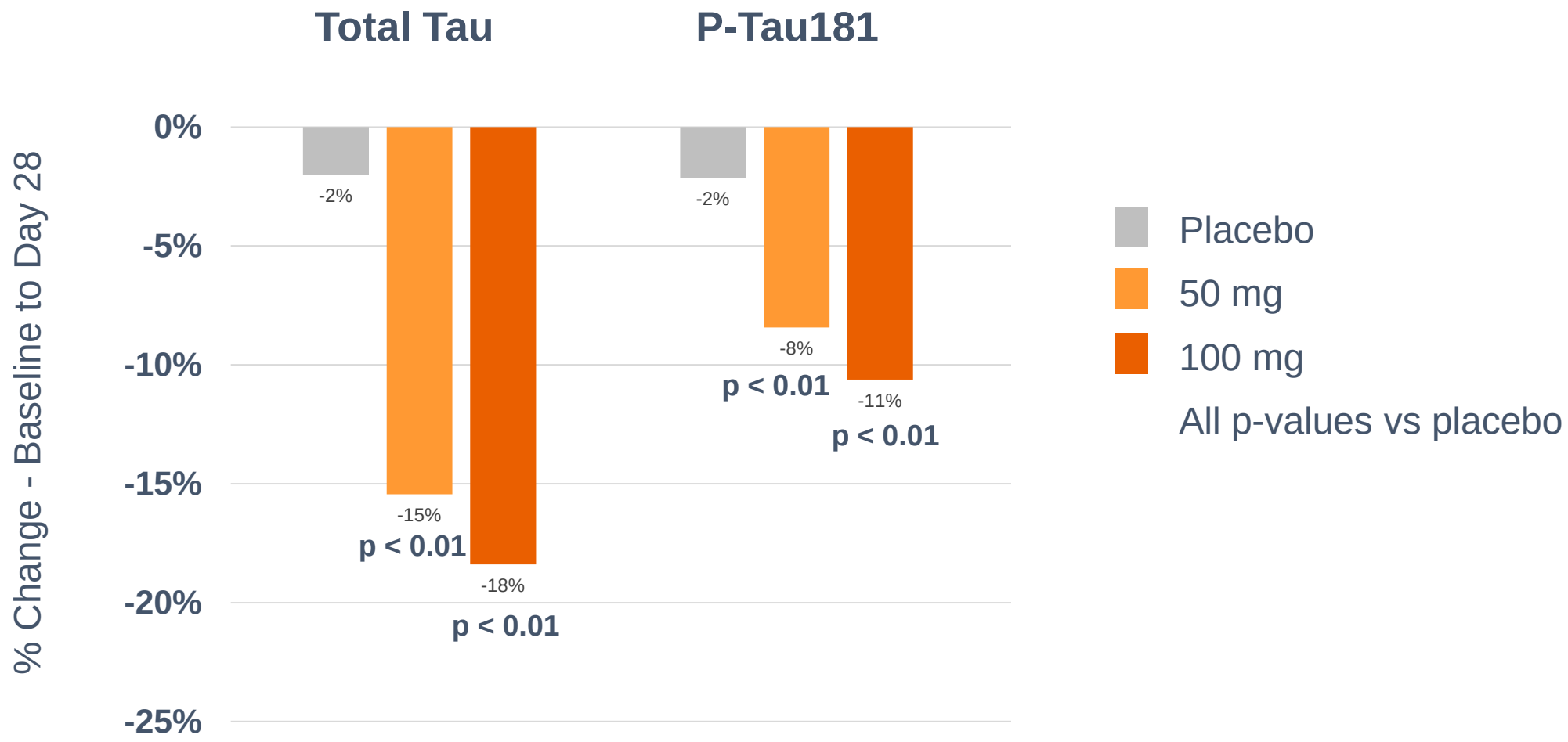
Phase 2b - AD Pathology Decreased Significantly

Levels of CSF Tau Proteins Decreased Significantly in Both Drug Groups



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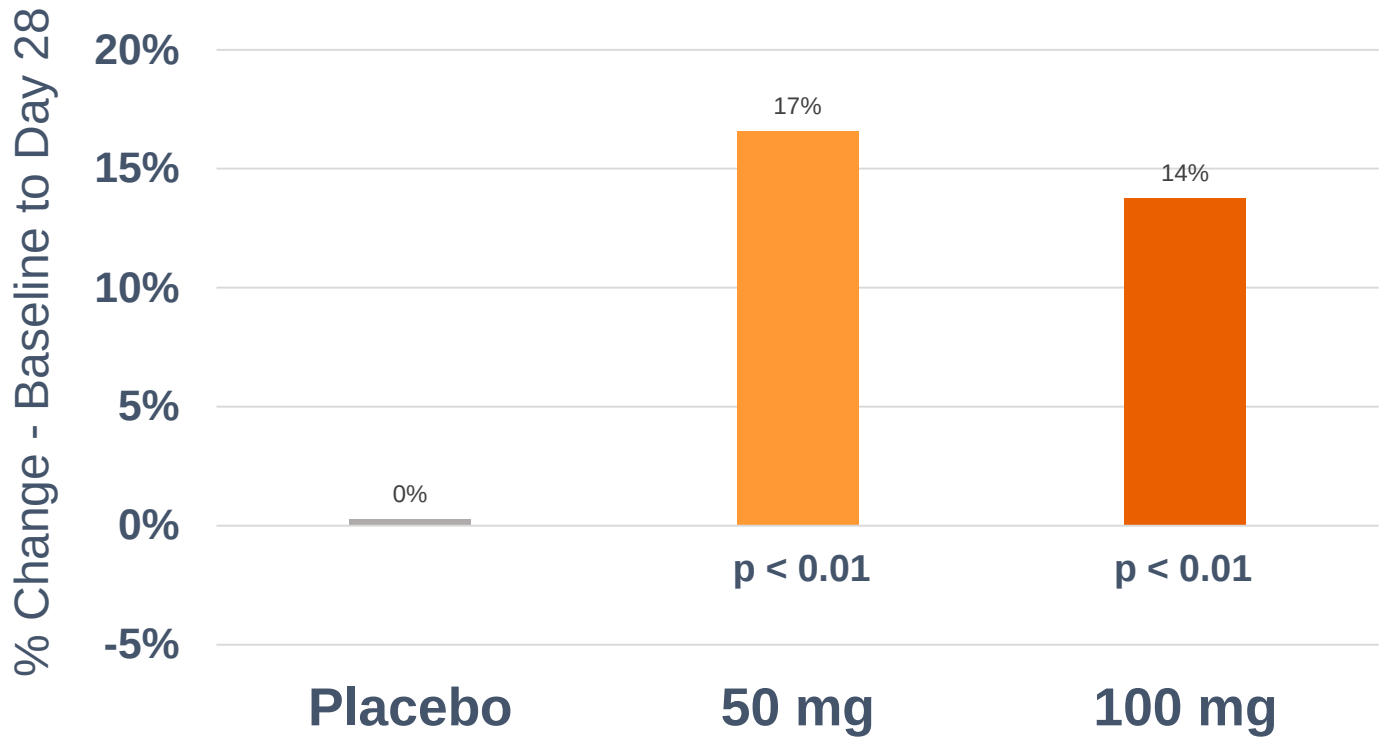
Phase 2b - $A\beta_{42}$, Low in AD, Increased Significantly

Change in Levels of CSF Amyloid-β_{42} Day 0 to Day 28



Note: CSF amyloid-β_{42} levels are low in early stages of dementia in patients with Alzheimer's disease.

All p-values vs placebo

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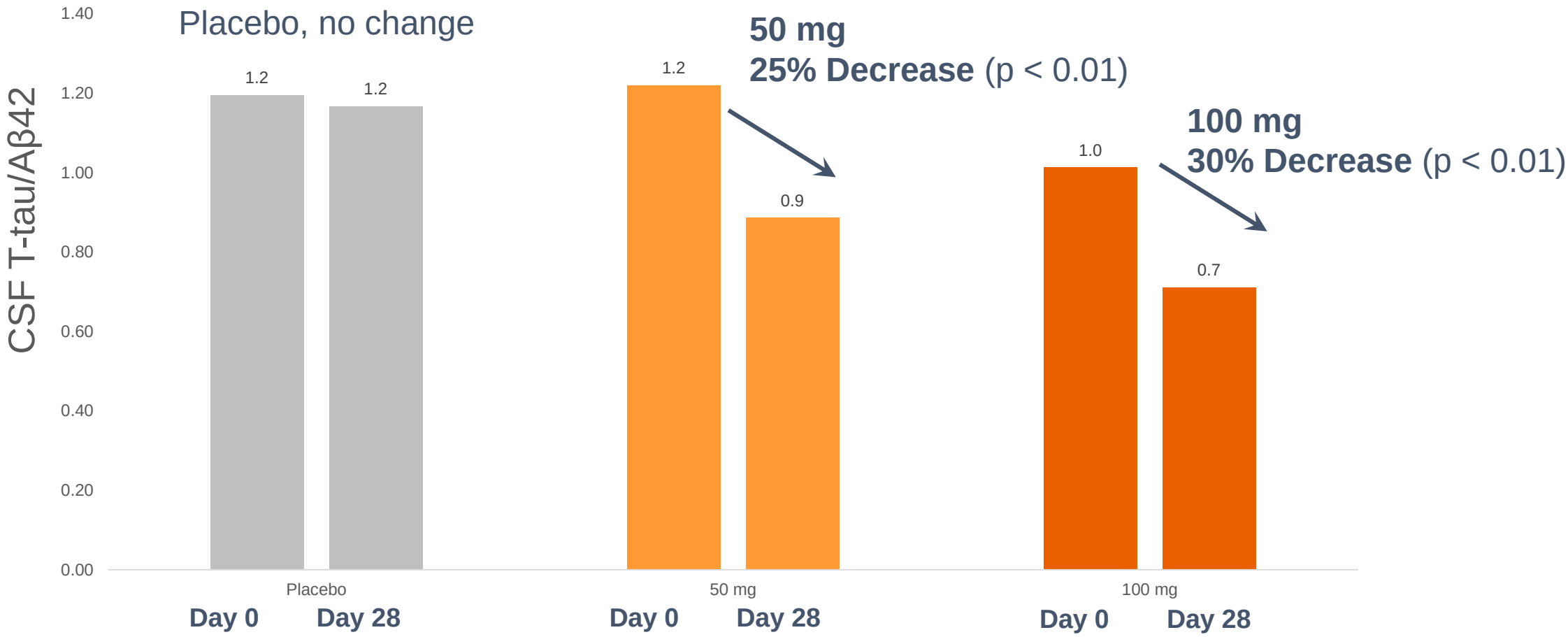
Phase 2b - Total tau/Aβ$_{42}$ Dropped Significantly

A Key Diagnostic Criteria for AD Decreased Significantly in Both Drug Groups

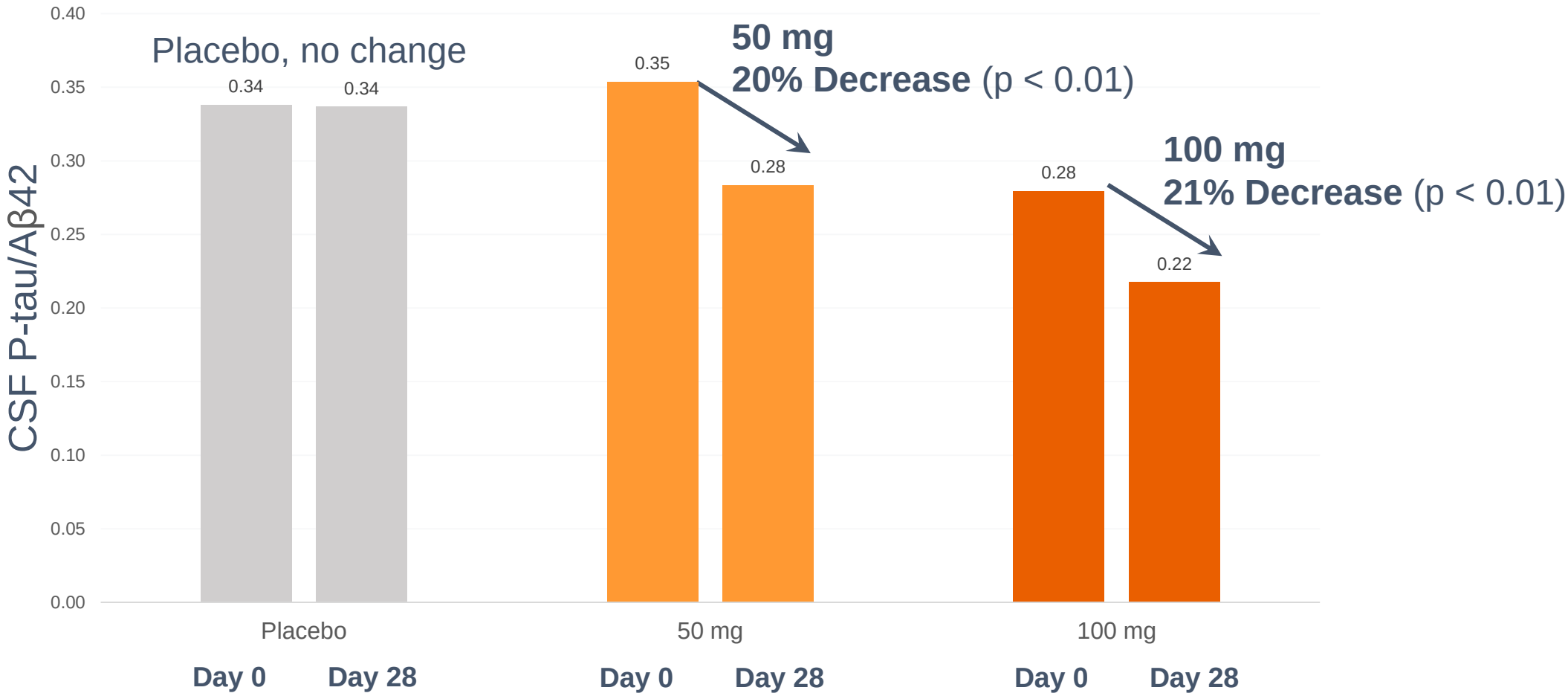
Change in Ratio of CSF T-tau/Aβ$_{42}$ Day 0 to Day 28



Phase 2b - P-tau/Aβ$_{42}$ Dropped Significantly

A Key Diagnostic Criteria for AD Decreased Significantly in Both Drug Groups

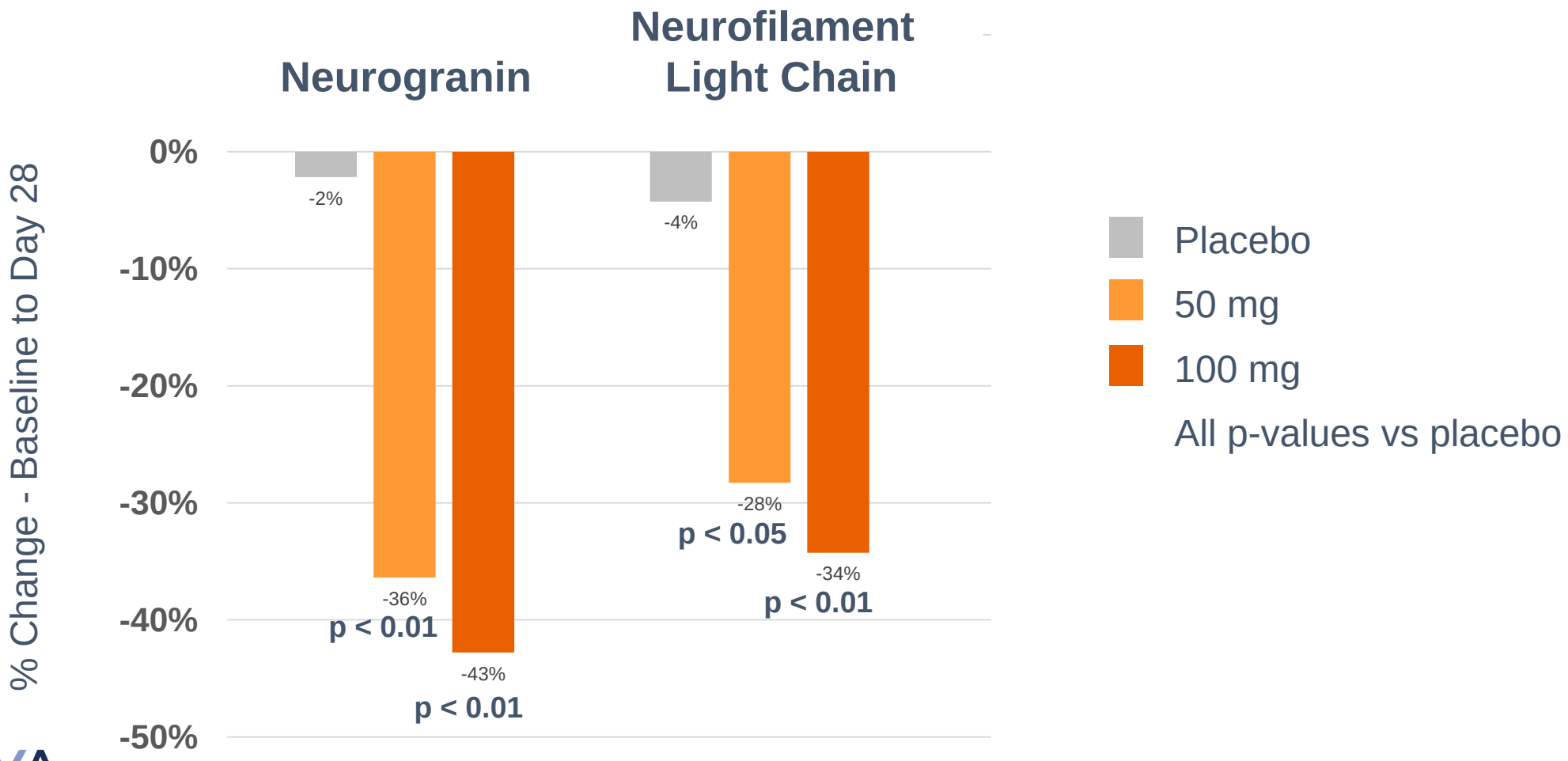
Change in Ratio of CSF P-tau/Aβ$_{42}$ Day 0 to Day 28



Phase 2b - Neurodegeneration Decreased

Biomarkers of Neurodegeneration Decreased Significantly in Both Drug Groups

Change in Levels of CSF Ng and NfL Day 0 to Day 28



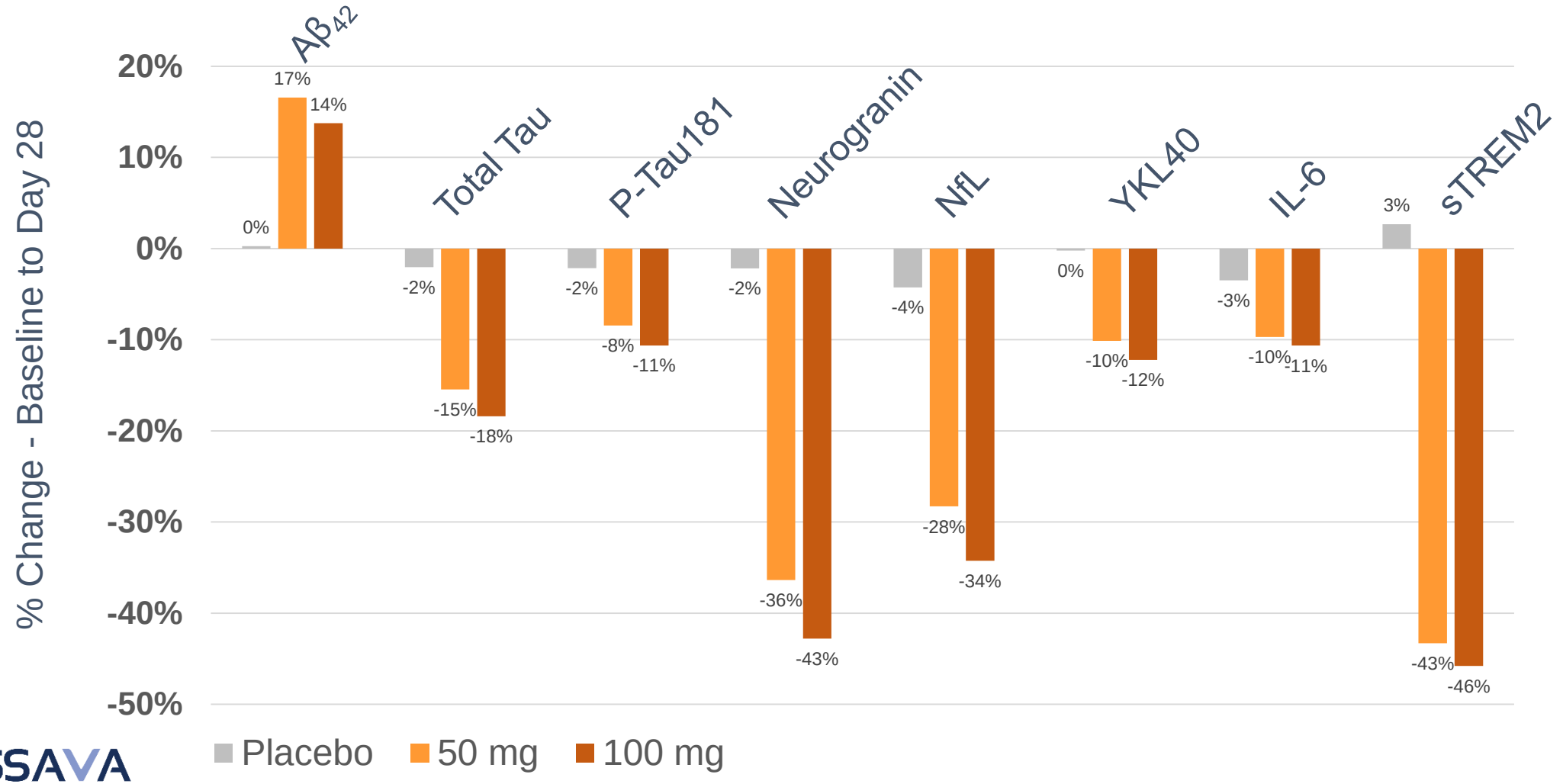
Phase 2b - Neuroinflammation Decreased

Biomarkers of Neuroinflammation Decreased Significantly in Both Drug Groups

Change in Levels of CSF YKL-40, IL-6 and soluble TREM2, Day 0 to Day 28

Phase 2b - Summary of CSF Results

Sumifilam Significantly Improved An Entire Panel of AD-related Biomarkers



Phase 2b - Cognition

- **CANTAB (Cambridge Neuropsychological Test Automated Battery) is a widely used, computer-based battery of memory tests sensitive to subtle changes in cognition.**
  - Tests are independent of language skills, speed, gender or education.

- **Cognitive assessments were made on Day 1 (pre-dose) and again on Day 28.**

- **Patients were tested on ‘episodic memory’ and ‘spatial working memory’.**
  - Patients advance through progressively more difficult levels.
  - Outcome measure = total errors, with errors imputed for more difficult levels not reached, so…….

Lower score is better!

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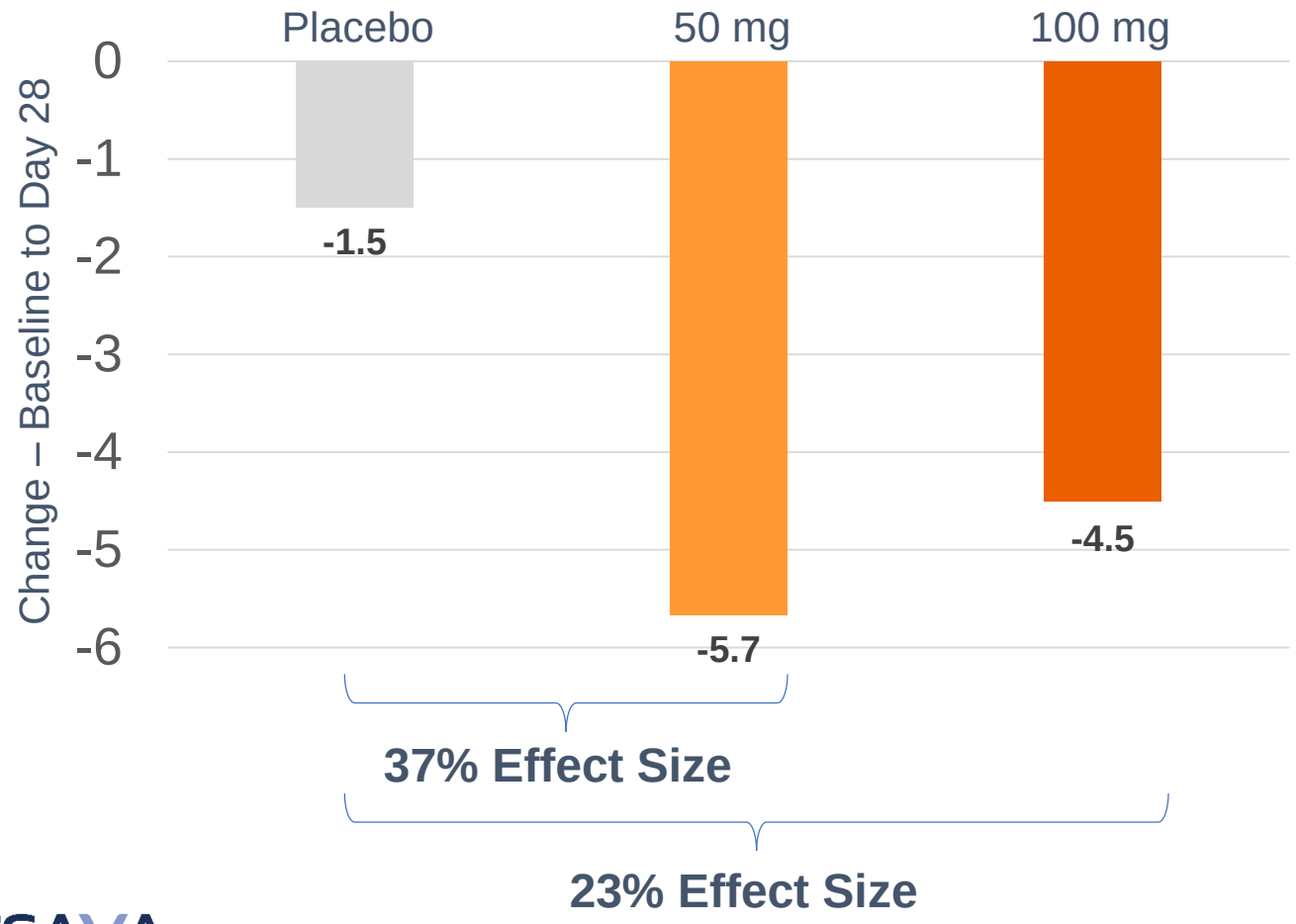
Phase 2b - Cognition

Drug Groups Show Directional Improvements in Episodic Memory



Episodic Memory Endpoint:

- **Lower score is better** on change from baseline in Total Errors on Paired Associates Learning (PAL).
- Effect sizes vs. placebo were calculated by Hedge's g after removing the most and least impaired subjects across all groups by baseline score.
- Effect size measures the magnitude of effect; in contrast, statistical significance measures the probability of effect occurring by chance.

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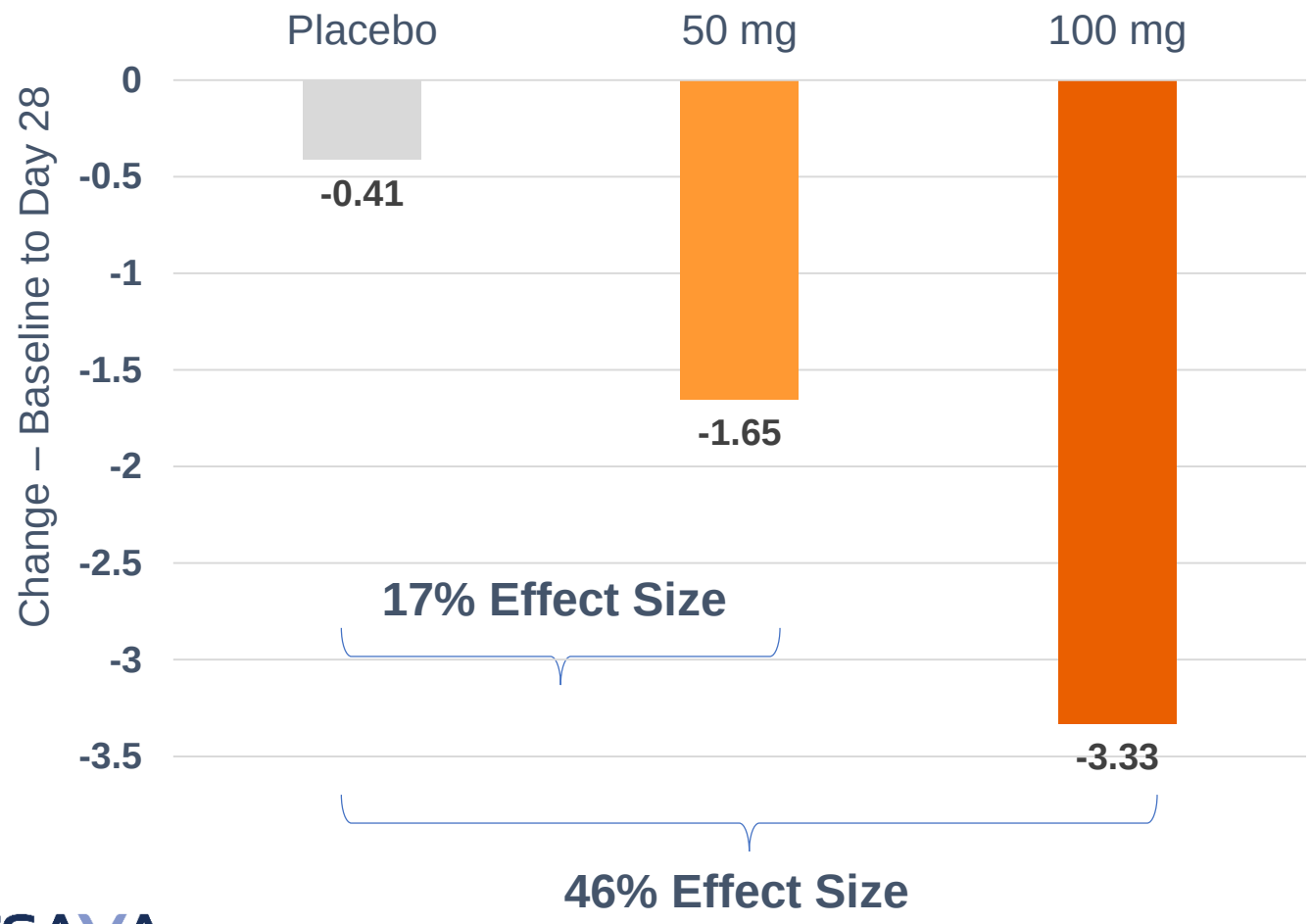
Phase 2b - Cognition

Drug Groups Show Directional Improvements in Spatial Working Memory



Spatial Working Memory Endpoint:

- **Lower score is better** on change from baseline in Total Errors on Spatial Working Memory task.
- Effect sizes vs. placebo were calculated by Hedge's g.
- Patients who did not take drug (no blood levels) were removed.

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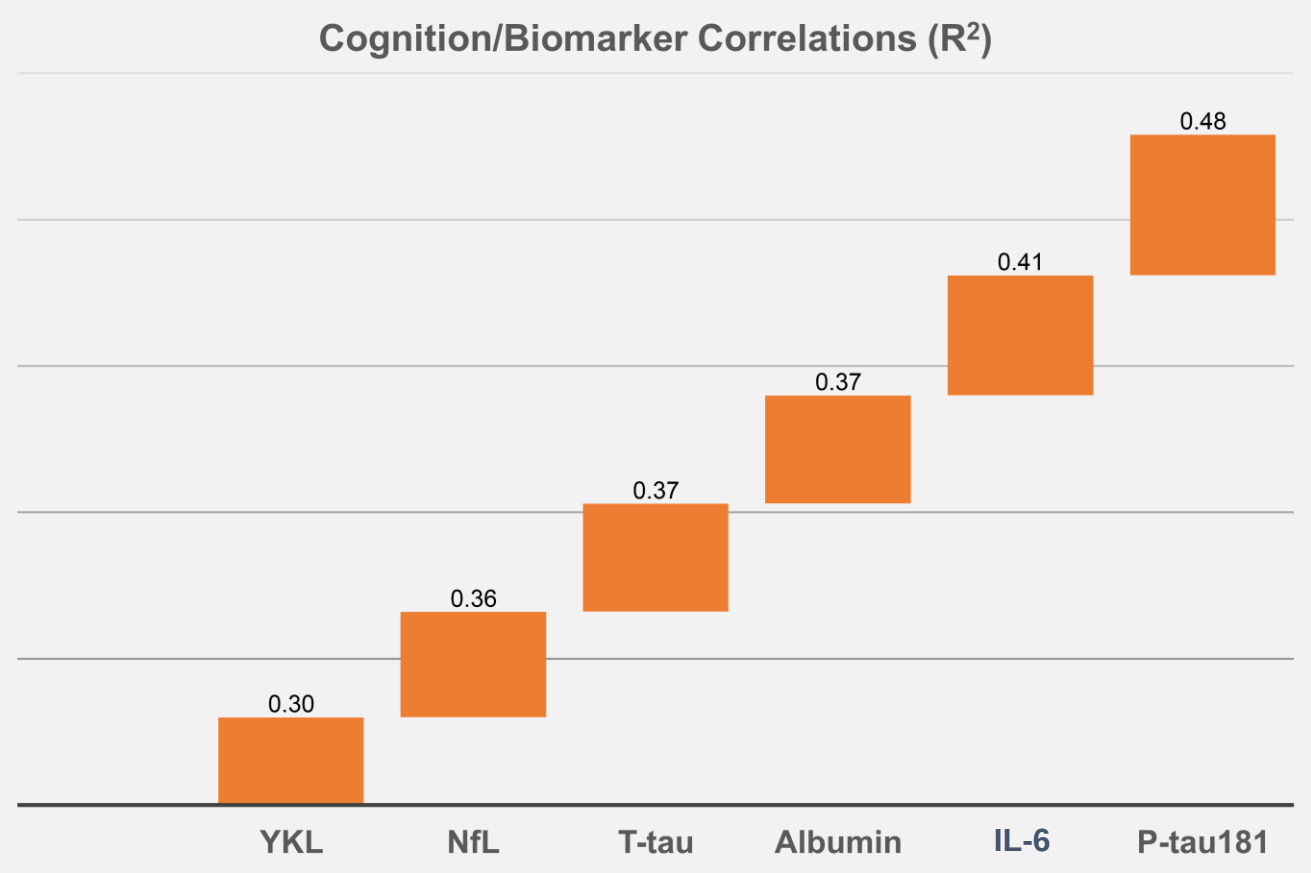
Phase 2b - Cognition/Biomarker Correlation

Cognitive Improvement Correlates Most ($R^2 = 0.5$) With Decreases in CSF P-tau181



Summary of Drug Effects

- **98% of patients treated with sumifilam 50 mg or 100 mg b.i.d. for 28 days showed improvements in validated biomarkers of AD pathology; neuroinflammation; and neurodegeneration; with no safety issues.**

- **Sumifilam appears to stabilize or improve memory.**
  - 37% and 23% effect sizes in episodic memory vs placebo
  - 17% and 46% effect sizes in spatial working memory vs placebo
  - Improved cognition correlated most strongly with reduction in levels of P-tau^{181} (R^2 = 0.5)

- **Target engagement and mechanism of action were demonstrated in prior clinical and non-clinical studies and was demonstrated again in this Phase 2b.**

These data validate FLNA as a promising new therapeutic target for AD.

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Conclusions & Next Steps

Remi Barbier, President & CEO

Eric Schoen, Chief Financial Officer

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Conclusions

- **A well-controlled Phase 2b study of sumifilam showed promising treatment effects in mild-to-moderate AD patients.**
  - No other clinical-stage drug candidate has improved an entire panel of biomarkers of disease pathology, neurodegeneration and neuroinflammation, and appears to benefit cognition.

- **Phase 2b drug effects are consistent with Phase 2a clinical results, preclinical data, mechanism of action and basic research.**

- **The dataset highlight sumifilam's potential as a disease-modifying drug candidate for Alzheimer's disease.**

Clinical data will need to be replicated in large, Phase 3 efficacy studies.

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Next Steps - Replicate Drug Effects in Phase 3

- Phase 2b publication, peer-reviewed journal.
- End-of-phase 2 (EOP2) meeting with FDA.
- Complete patient enrollment in on-going, open-label study of sumifilam.
- Develop study plan for Phase 3 efficacy program in Alzheimer's disease.
- Manufacture Phase 3 clinical trial supplies (drug substance + oral tablets).
- Initiate Phase 3 efficacy program, estimated 2021+

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Intellectual Property

- **Sumifilam was discovered in-house. Cassava Sciences owns exclusive, worldwide rights to this and other drug asset and related technologies, without milestone or royalty obligations to any third party.**

- **Sumifilam is a novel molecule. Cassava Sciences owns composition of matter claims on sumifilam and other novel, filamin-binding molecules.**

- **Cassava Sciences' patent protection in this area currently runs beyond 2037, plus extensions, and includes seven issued patents and related patent filings and applications.**

Key Financials

Nasdaq ticker: SAVA	
Shares Outstanding	24.9 million
Warrants Outstanding	1.4 million
Total Shares Outstanding =	***26.3 million***
Unaudited Financials	
Cash Balance at June 30, 2020	≈ $25.3 million
Expected Net Cash Use Full-year 2020	≈ $ 5.0 million
No Debt	

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Clinical Discussion with Dr. Gonzalez-Rojas, MD, Principal Investigator

Yaneicy Gonzalez-Rojas MD, Internal Medicine, is an ACRP-certified Principal Investigator working in Coral Gables, FL. Besides being an established medical practitioner treating hundreds of Alzheimer's patients annually, she has a keen interest in conducting quality clinical trials. Dr. Gonzalez-Rojas has participated in 13 clinical trials of various investigational drug agents for Alzheimer's disease, including sumifilam.

Q & A Session

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Appendix: Key Publications

Journal of Prevention of Alzheimer's Disease
2020; DOI: 10.14283
PTI-125 Reduces Biomarkers of Alzheimer's Disease In Patients:
http://link.springer.com/article/10.14283/jpad.2020.6

Neuroimmunology and Neuroinflammation
2017;4:263-71:
Altered filamin A enables amyloid beta induced tau hyperphosphorylation and neuroinflammation in Alzheimer's disease:
http://nnjournal.net/article/view/2313

Neurobiology of Aging
(Volume 55) July 2017, Pages 99—114)
PTI-125 binds and reverses an altered conformation of filamin A to reduce Alzheimer's disease pathogenesis:
http://www.neurobiologyofaging.org/article/S0197-4580(17)30087-8/

Alzheimer's & Dementia
Volume 8, Issue 4, Supplement, 1 July 2012, Pages p259-p260
PTI-125 reduces amyloid-related Alzheimer's pathogenesis by targeting filamin A:
https://www.sciencedirect.com/science/article/pii/S1552526012008242

Journal of Neuroscience
18 July 2012, 32 (29) 9773-9784
Reducing amyloid-related Alzheimer's disease pathogenesis by a small molecule targeting filamin A
http://www.jneurosci.org/content/32/29/9773.short

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Appendix - Biomarkers Generally Correlate!

AD biomarkers generally move in tandem as disease progresses. Therefore, a valid and sound bioanalysis should show data from placebo patients with robust statistical correlations among changes in biomarkers.

The first bioanalysis showed no correlation in the placebo samples (R^2=0.06, on average).

Correlation Values (R^2) Between Changes in CSF Biomarkers.
Placebo patients only – Baseline vs. Day 28.

	Total Tau	P-tau181	NfL	Ng	YKL40	IL-6
Total Tau	1.00	0.41	0.07	0.39	0.25	-0.05
P-tau181	0.41	1.00	-0.13	0.00	-0.04	0.26
NfL	0.07	-0.13	1.00	-0.05	-0.16	-0.07
Ng	0.39	0.00	-0.05	1.00	0.43	-0.21
YKL40	0.25	-0.04	-0.16	0.43	1.00	-0.15
IL-6	-0.05	0.26	-0.07	-0.21	-0.15	1.00