



We Focus on Alzheimer's disease

April 2021

Forward-Looking Statements & Safe Harbor

This presentation contains forward-looking statements, including statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, relating to: our strategy and plans; the treatment of Alzheimer's disease; the status of current and future clinical studies with simufilam, including the interpretation of interim analyses of open-label study results; changes to the open-label study, including future interim analyses; our intention to initiate a Cognition Maintenance Study and a Phase 3 clinical program with simufilam in 2021; results of our EOP2 meeting with FDA; our ability to manufacture drug supply for a Phase 3 program; results of a validation study with SavaDx; our ability to expand therapeutic indications for simufilam outside of Alzheimer's disease; expected cash use in future periods; plans to publish results of a Phase 2b study in a peer-reviewed journal; verbal commentaries made by our employees; and potential benefits, if any, of the our product candidates. These statements may be identified by words such as "may," "anticipate," "believe," "could," "expect," "forecast," "intend," "plan," "possible," "potential," and other words and terms of similar meaning.

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Cassava Sciences Highlights

- Our goal is to defeat Alzheimer's disease.
- Alzheimer's disease is one of the greatest unmet medical needs, with no disease-modifying medicines.
- Our scientific approach is unique, our clinical data is highly differentiated.
- Our science programs have been developed with scientific and financial support from the National Institutes of Health (NIH).
- We are developing **simufilam**, a proprietary drug candidate to treat Alzheimer's disease and SavaDx, a blood-based investigational diagnostic.
- Simufilam is Phase 3 ready in 2021.
- Key drivers of our clinical development program:
 - » A decade of research in basic biology
 - » Clear scientific rationale
 - » Published pre-clinical results
 - » Well-understood mechanism of action
 - » Clean safety profile
 - » Evidence of target engagement in patients
 - » Unprecedented CSF biomarker data
 - » Phase 2b clinical results
 - » Early data on cognition and behavior
 - » Successful End-of-Phase 2 meeting with FDA

Meet the Team



Remi Barbier - Chairman, President & CEO



Lindsay H. Burns, PhD - SVP Neuroscience



Nadav Friedmann, PhD/MD - CMO, Board member
Eight FDA drug approvals prior to Cassava Sciences.



Michael Zamloot - SVP Technical Operations
Four FDA drug approvals prior to Cassava Sciences.



Jim Kupiec, MD – Chief Clinical Development Officer
Two FDA drug approvals prior to Cassava Sciences.



Eric Schoen - Chief Financial Officer



Independent Directors



Sanford Robertson

- Founding Partner - Francisco Partners
- Founder & Chairman - Robertson, Stephens & Company



Robert Gussin, PhD

- Formerly, Johnson & Johnson, Chief Scientific Officer and Corporate VP, Science and Technology



Patrick Scannon, MD/PhD

- Formerly, Founder & CSO/CMO - XOMA Corporation

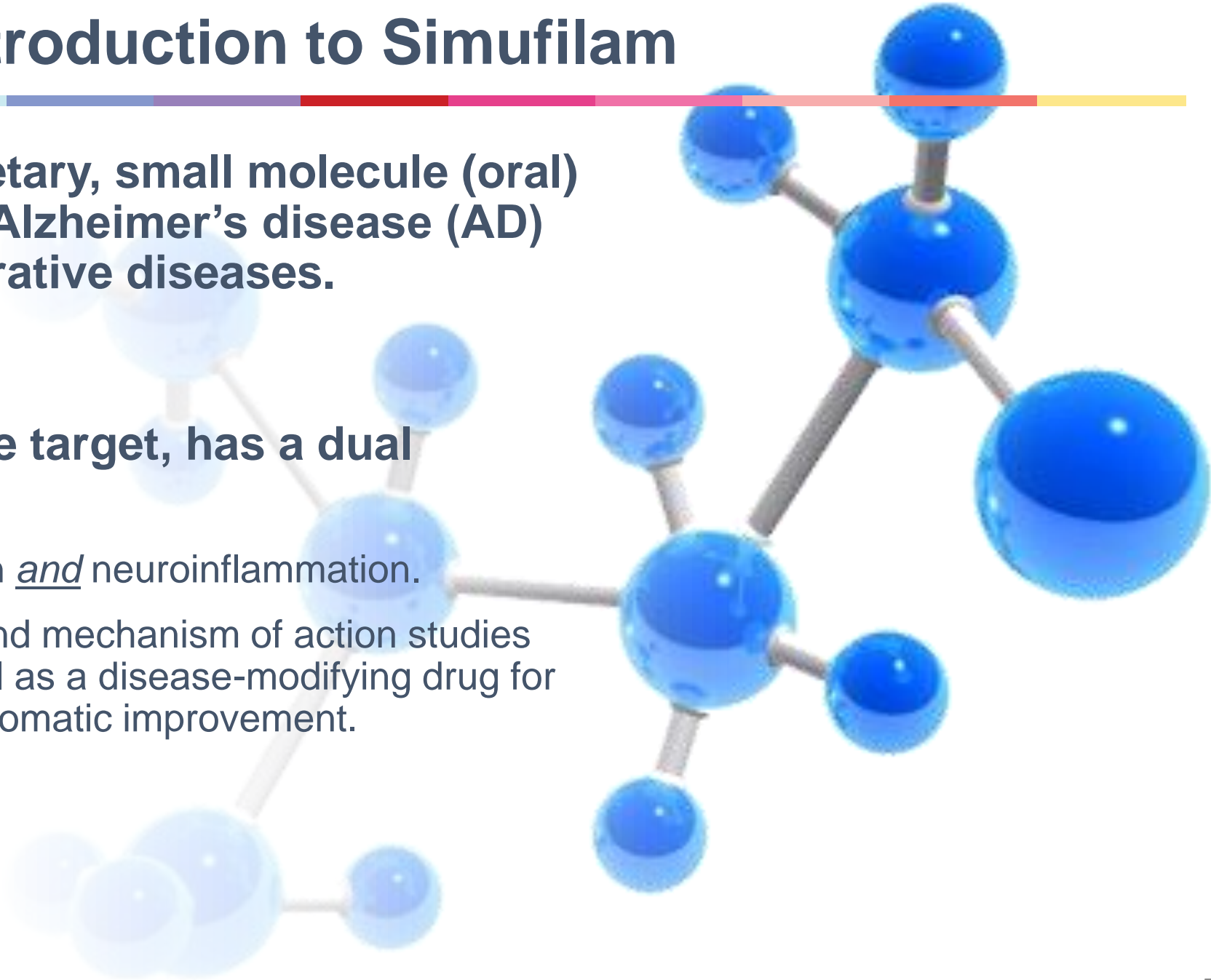


Michael O'Donnell

- Partner, Morrison & Foerster LLP

Introduction to Simufilam

- Simufilam is our proprietary, small molecule (oral) drug candidate to treat Alzheimer's disease (AD) and other neurodegenerative diseases.
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- Simufilam binds a single target, has a dual mechanism of action:
 - Reduces neurodegeneration and neuroinflammation.
 - Published preclinical data and mechanism of action studies support simufilam's potential as a disease-modifying drug for AD that also provides symptomatic improvement.



Clinical Development Progress

- ✓ *2017: simufilam is safe, well-tolerated in human volunteers.*
- ✓ *2019: positive results on CSF biomarkers of disease in an open-label, Phase 2a study of simufilam in AD patients.*
- ✓ *2020: positive results on CSF biomarkers of disease in a randomized, placebo-controlled Phase 2b study of simufilam in AD patients.*
- ✓ *2021: positive results on cognition in a 6-month interim analysis of an on-going, open-label study in AD patients. Successful End-of-Phase 2 meeting with FDA.*

We plan to initiate a Phase 3 study of simufilam in Alzheimer's disease in 2nd half 2021.

Science & Technology

Lindsay Burns, PhD – SVP Neuroscience

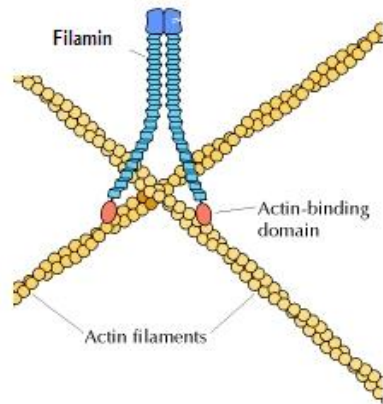
Nadav Friedmann, PhD/MD – Chief Medical Officer

Jim Kupiec, MD - Chief Clinical Development Officer

Simufilam Mechanism of Action

The Target of Simufilam 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.

Mechanism of Action

The altered form of FLNA is a proteopathy in the AD brain.

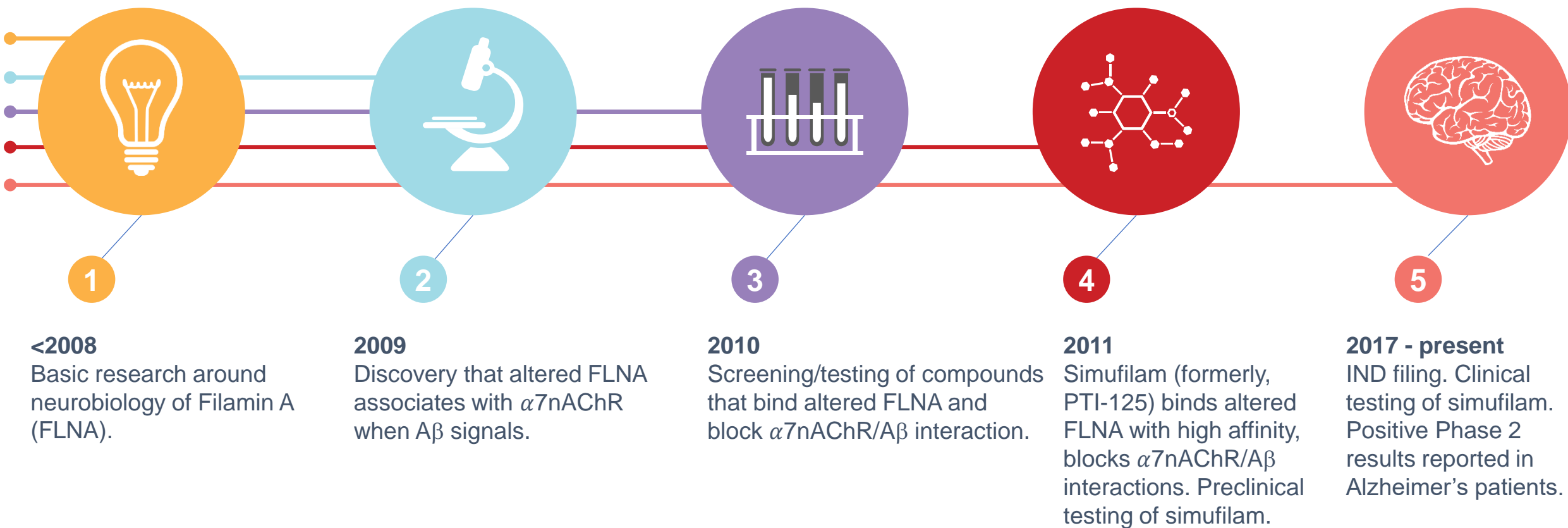
Altered FLNA enables $A\beta_{42}$ signaling via:

- i. $\alpha 7$ -nicotinic acetylcholine receptor ($\alpha 7$ nAChR)
→ hyperphosphorylates tau
- ii. Toll-like receptor 4 (TLR4)
→ releases inflammatory cytokines

Simufilam binds altered FLNA, restores its proper shape/function, disables $A\beta_{42}$ signaling via $\alpha 7$ nAChR and TLR4.

***Through a single target,
simufilam reduces neurodegeneration and neuroinflammation.***

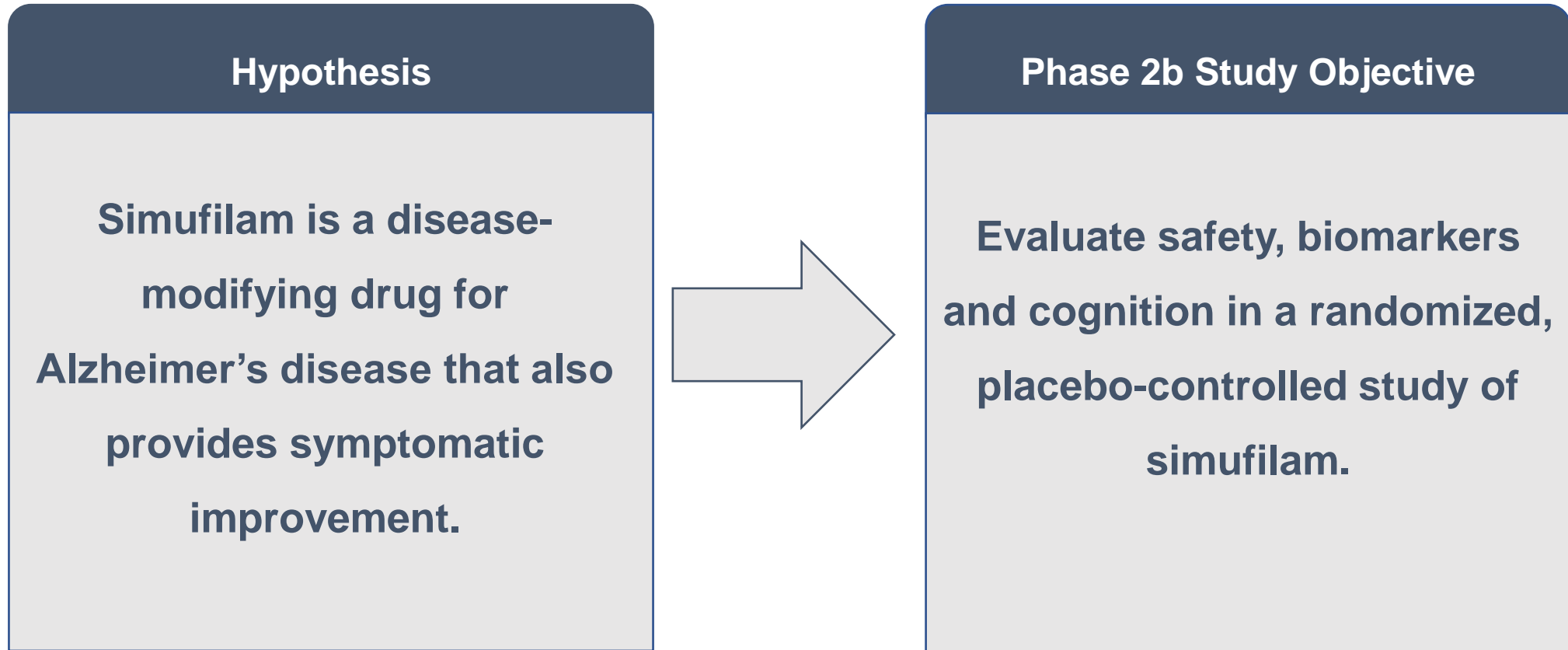
10+ Year In-house Discovery/Development Program



Summary of Preclinical Effects

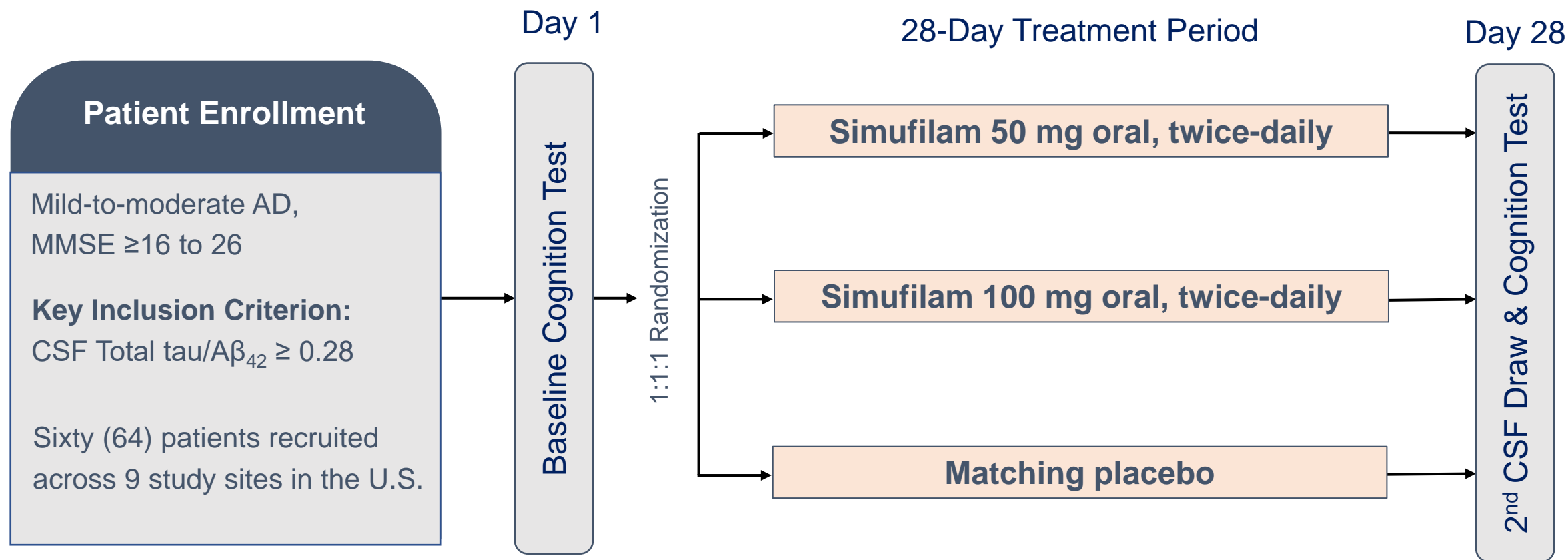
Simufilam	Intracerebro-ventricular (ICV) Aβ_{42} infusion mouse model	Triple transgenic AD mouse model	Post-mortem human AD brain tissue	Post-mortem human age-matched control brain tissue treated with Aβ_{42} in vitro
Reduced FLNA linkage to $\alpha 7$ nAChR/TLR4	✓	✓	✓	✓
Reduced A β_{42} bound to $\alpha 7$ nAChR	✓	✓	✓	✓
Reduced amyloid deposits and NFTs	✓	✓		
Reduced tau hyperphosphorylation	✓	✓		✓
Improved function of $\alpha 7$ nAChR, NMDAR and insulin receptors	✓	✓	✓	✓
Improved synaptic plasticity (activity-dependent Arc expression)		✓		✓
Reduced inflammatory cytokine levels	✓	✓		
Improved cognition/behavior		✓		

Clinical Hypothesis



Phase 2b - Study Design

Double-blind, Randomized, Placebo-controlled, Multi-center Study



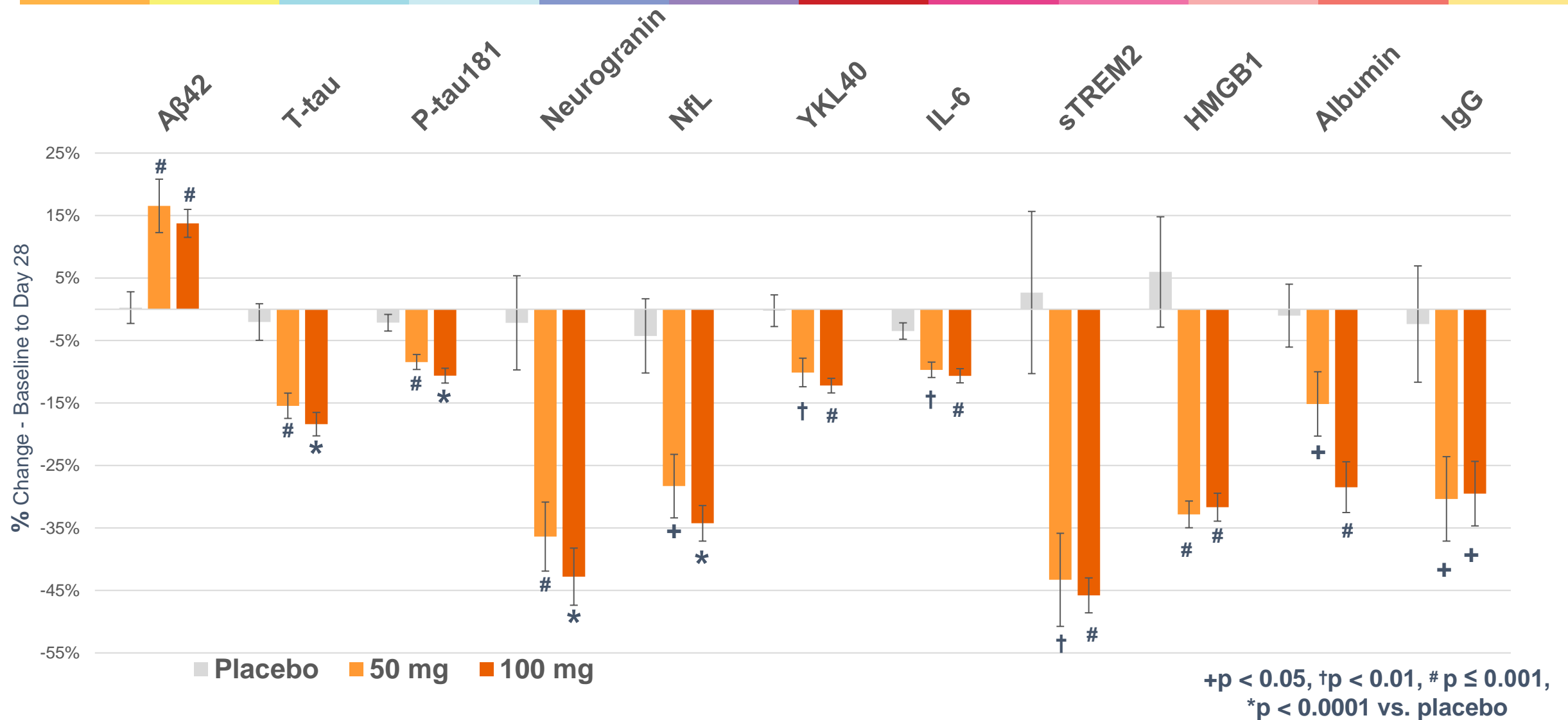
Primary Endpoint: **Biomarkers of disease**

Secondary Endpoint: **Cognition**

Phase 2b Results – Safety & Baseline

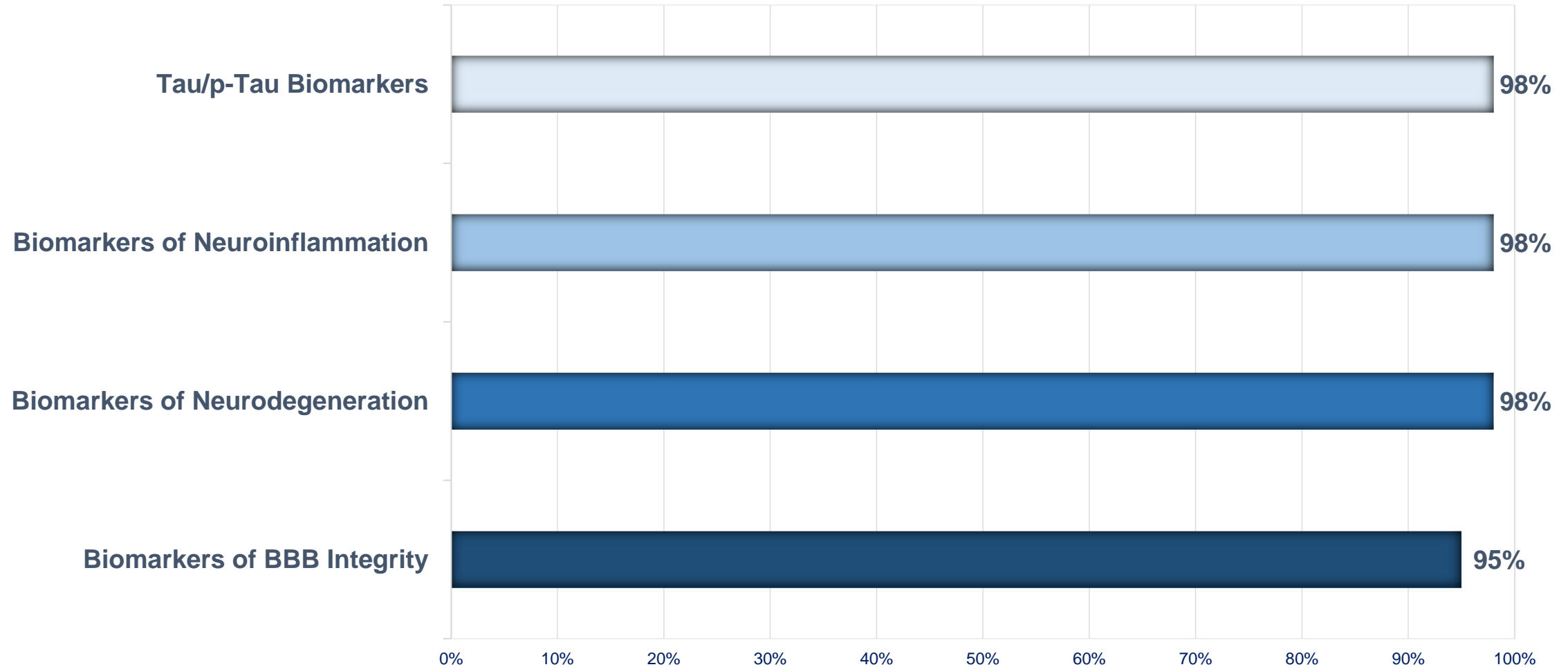
- **Simufilam was safe and well-tolerated**
- **No serious adverse events**
- **No drug-related patient discontinuation**
- **No drug-related adverse events**
 - Common, non-persistent side-effects observed in placebo & drug groups
- **Baseline characteristics were well-balanced between treatment groups, assigned through (1:1:1) randomization.**

Phase 2b Summary of Results - CSF Biomarkers



Phase 2b Results – Patient Responder Analysis

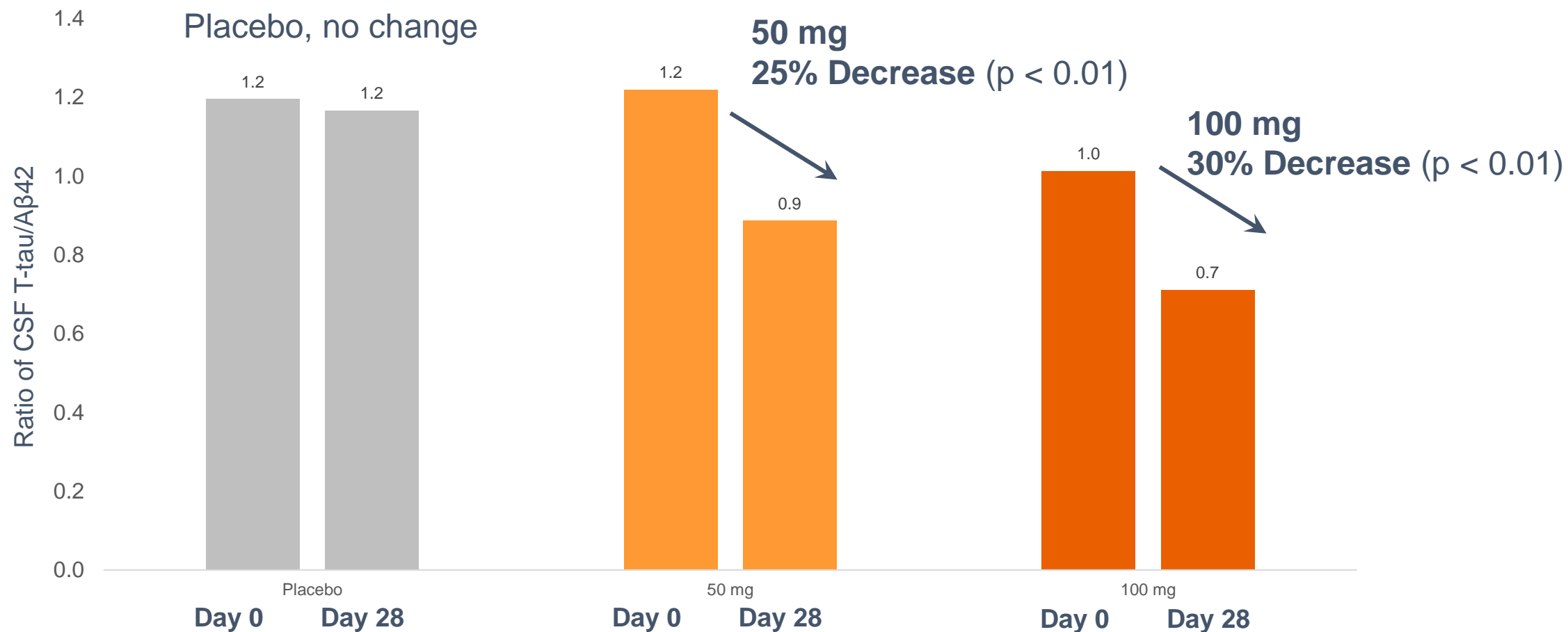
% of Patients Who Responded to Simufilam on CSF Biomarkers



Phase 2b Results - Total tau/A β_{42} Decreased Significantly

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

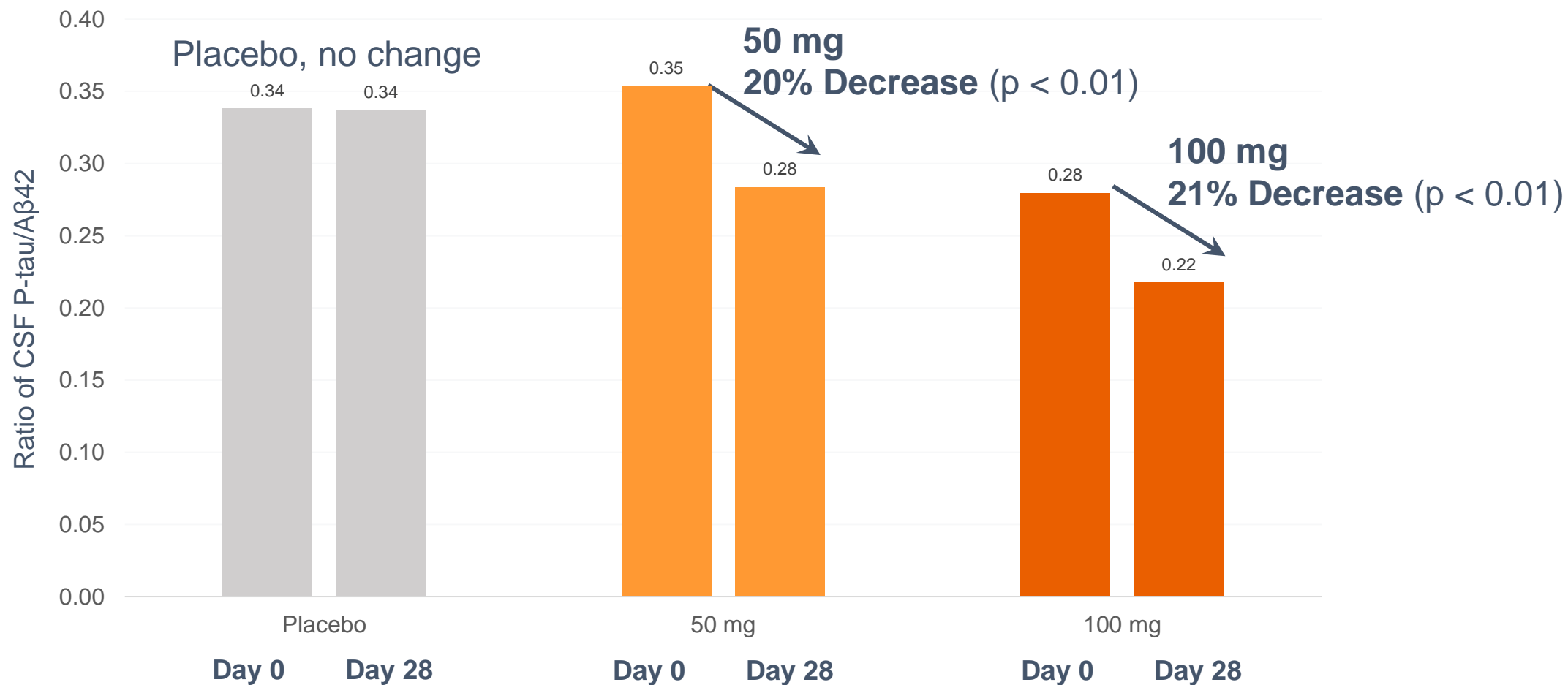
Change in Ratio of CSF T-tau/A β_{42} Day 0 to Day 28



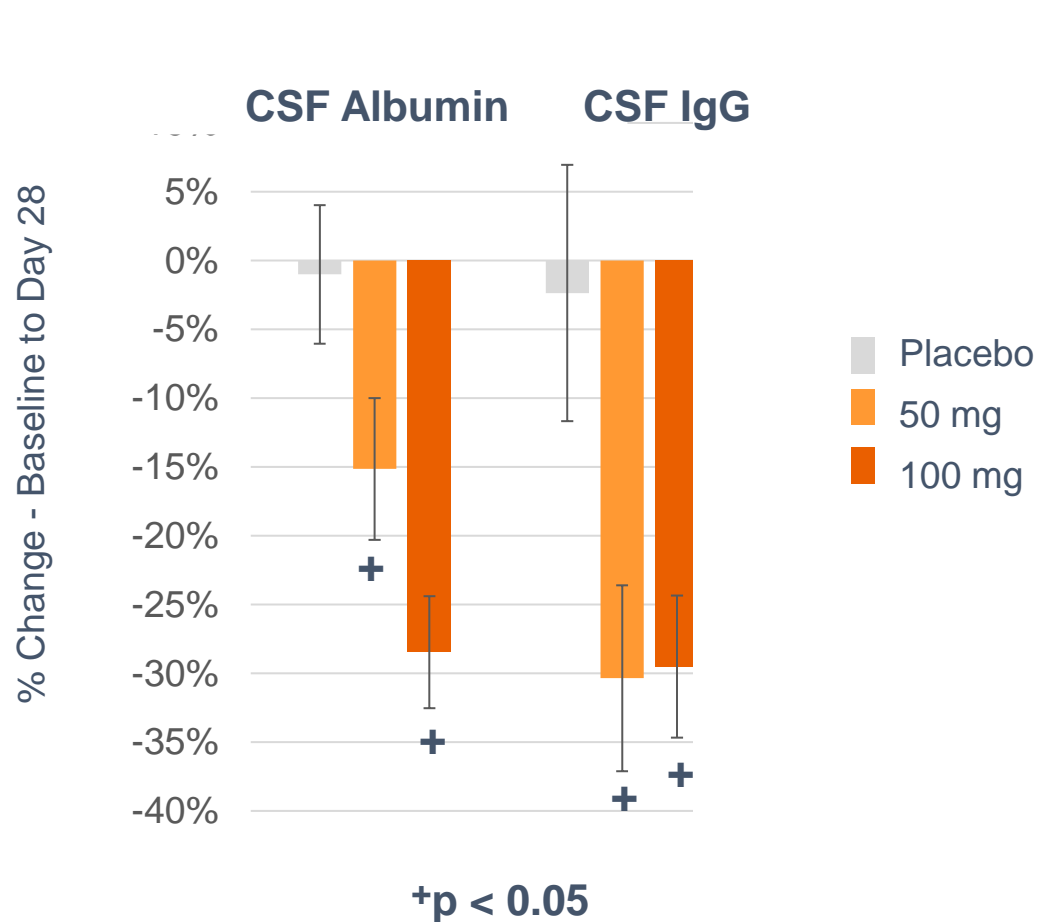
Phase 2b Results - P-tau/A β_{42} Decreased Significantly

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

Change in Ratio of CSF P-tau/A β_{42} Day 0 to Day 28



Phase 2b Results – Improved Blood-brain Barrier Integrity



**Albumin Ratio
by Treatment Group**

	Day 0	Day 28	Change
Placebo	24	24	No change
50 mg simufilam	25	20	- 5 (-20%)
100 mg simufilam	25	18	- 7 (-28%)

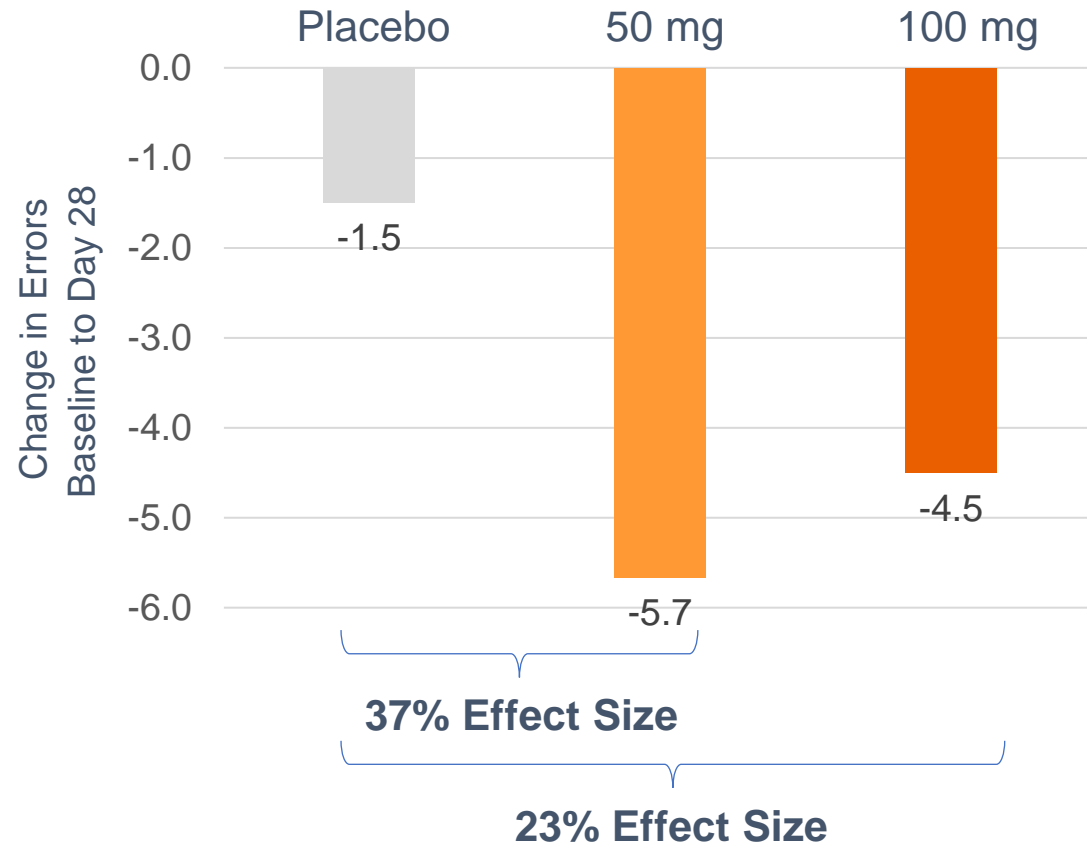
*Note: Albumin Ratio ((CSF/plasma)*100) is a clinical test for BBB permeability because albumin protein is not synthesized in CSF. Hence, albumin in CSF necessarily comes from plasma through the BBB.*

Cognition

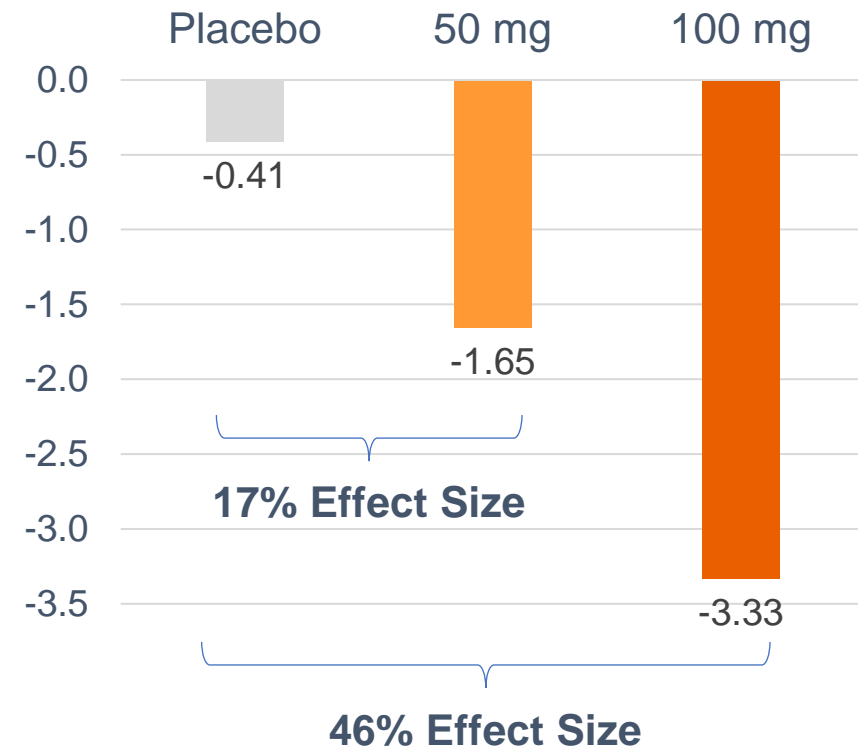
- **CANTAB** (Cambridge, England) is a validated, computer-based battery of memory tests that are sensitive to subtle changes in cognition.
 - Tests are independent of language skills, speed, gender or education.
- **Patients were assessed on ‘Episodic Memory’ and ‘Spatial Working Memory’.**
 - Patients advance through progressively more difficult levels.
 - Outcome measure = total errors, with errors imputed for more difficult levels not reached.
 - Lower score is better.
- **Patients were assessed on Day 1 (pre-dose) and Day 28.**

Phase 2b Results – Memory Measurements Improved

Episodic Memory Improved

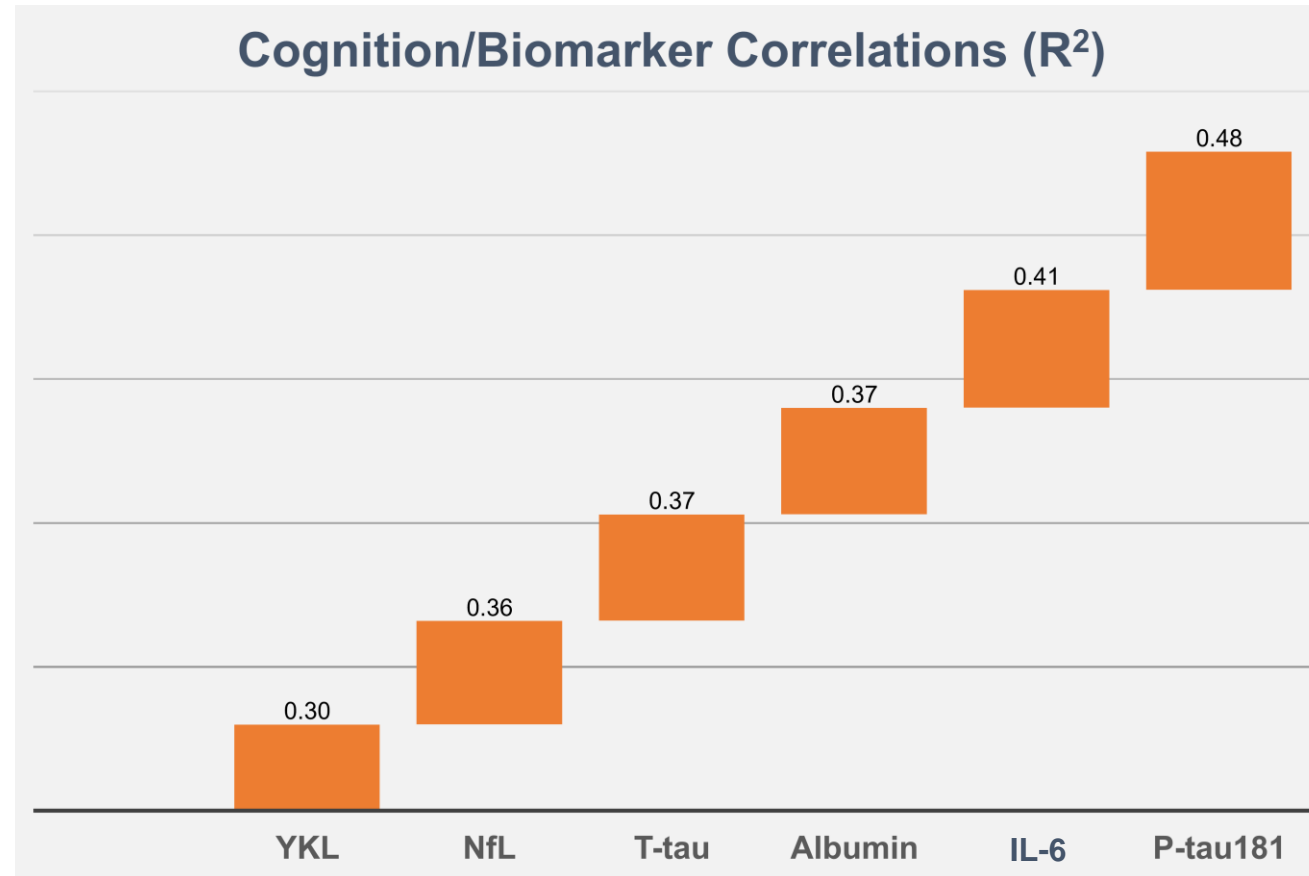


Spatial Working Memory Improved



Phase 2b Results - Cognition/Biomarker Correlation

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



Phase 2b Study Conclusions

- Simufilam showed promising treatment effects in a placebo-controlled study in patients with mild-to-moderate Alzheimer's disease.
- Simufilam improved a panel of validated biomarkers of disease pathology, neuroinflammation and BBB integrity.
- Simufilam appeared to enhance cognition.
- Phase 2b data replicate prior clinical results and are consistent with published preclinical data and mechanism of action studies.

Open-label Study

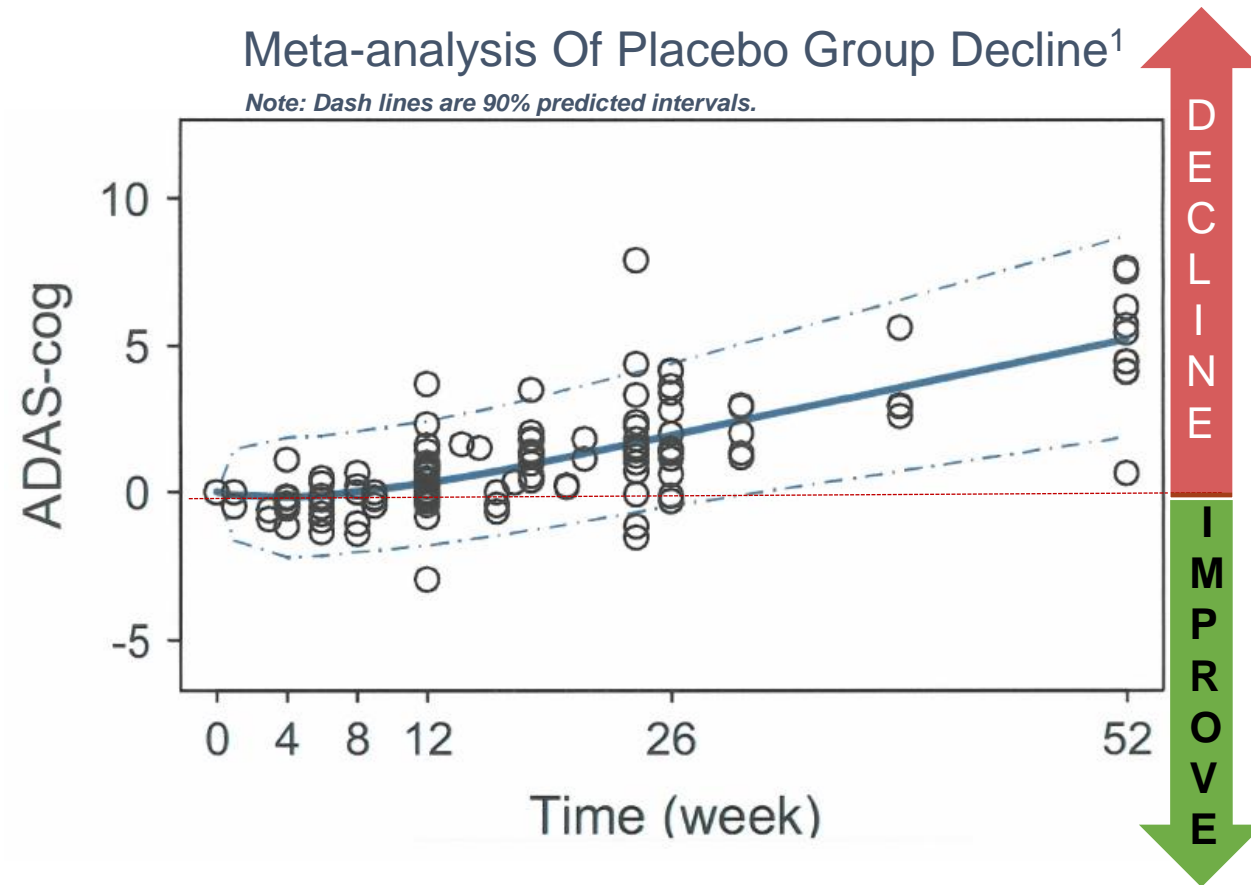
- **We are conducting an on-going one-year, open-label safety study of simufilam, with scientific and financial support from the National Institutes of Health (NIH).**
- **Patients are evaluated for safety, cognition and behavior.**
 - Cognition is evaluated on ADAS-Cog11.
 - AD-behavior is evaluated on NPI (Neuropsychiatric Inventory).
- **Target enrollment is 150 patients with mild-to-moderate AD.**
 - \approx 100 patients enrolled as of April 2021.

First Interim Analysis, Open-label Study

- **First interim analysis - first 50 patients who've completed 6 months of treatment.**
- **Simufilam improved cognition and behavior in Alzheimer's Disease.**
 - Cognition scores improved by 1.6 points on ADAS-Cog11, a 10% mean improvement from baseline to month 6.
 - Dementia-related behavior, such as anxiety, delusions and agitation, improved by 1.3 points on NPI, a 29% mean improvement from baseline to month 6.

Question: What Is The Expected Rate Of Cognitive Decline In AD Patients?

Expected Rate of Cognitive Decline in AD - Literature



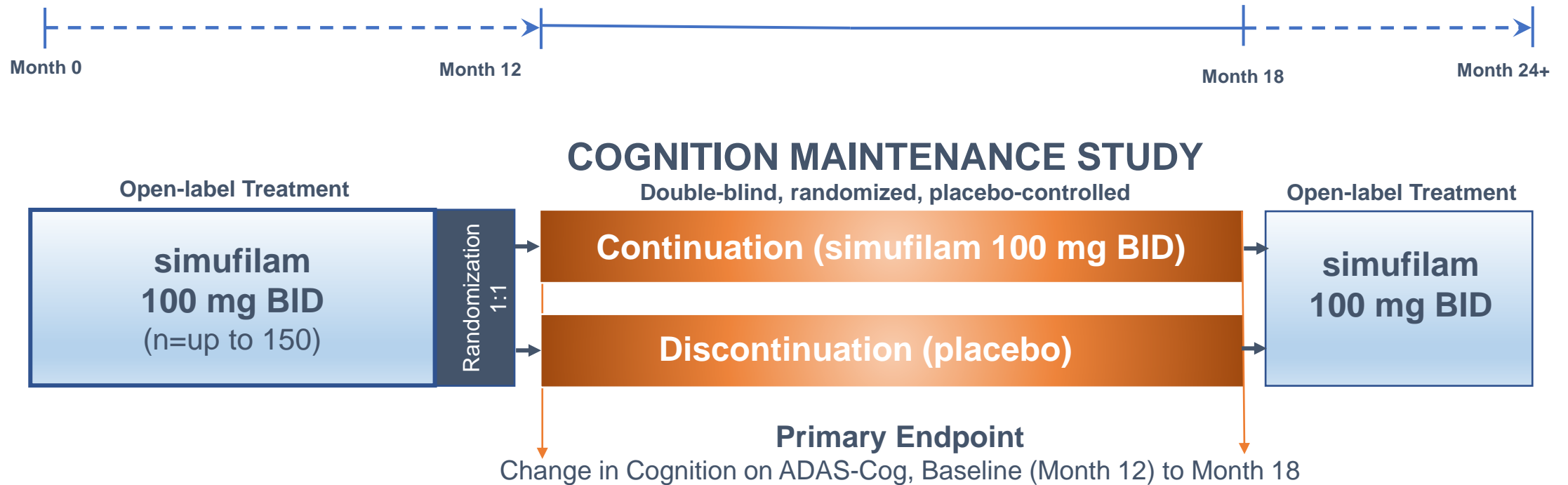
- Cognitive decline was reported in a meta-analysis of 20,000 patients with mild-to-moderate AD¹:
5.5 point decline/year on ADAS-Cog in placebo groups.
- Cognitive decline was reported in two P3 studies of Biogen's aducanumab in patients with early AD²:
5.2 point decline over 18 months on ADAS-Cog in placebo groups.

Upcoming Announcements - Interim Analyses

- **July 2021: announcement of clinical results on safety & cognition in patients who've completed at least 9 months of open-label treatment with simufilam.**
 - Data will be presented July 26 - 29th at the *2021 Alzheimer's Association International Conference (AAIC)* in Amsterdam, Netherlands.
 - AAIC's scientific committee has invited the Company's scientists to present the dataset as an oral presentation.
- **Sept 2021: announcement of clinical results on safety & cognition in patients who've completed at least 12 months of open-label treatment with simufilam.**

Cognition Maintenance Study

Goal is to compare cognition in AD patients who continue vs. discontinue simufilam following 1-year open-label treatment.



Initiation expected June 2021.

Regulatory Strategy

- **Successful End-of-phase 2 (EOP2) meeting was held with FDA January 14, 2021.**
 - EOP2 meeting objectives were to gain general agreement around a Phase 3 clinical program and statutory requirements for a 505(b)(1) NDA submission and marketing approval of simufilam for the treatment of mild-to-moderate Alzheimer's disease.
- **EOP2 official meeting minutes confirm alignment on critical elements of a Phase 3 program for simufilam.**
 - FDA agrees that the completed Phase 2 program, together with an upcoming and well-defined Phase 3 clinical program, are sufficient to show evidence of clinical efficacy.
 - Also, agreement on use of co-primary efficacy endpoints to assess cognition and function.

Phase 3 Program Overview

Our Phase 3 program consists of two double-blind, randomized, placebo-controlled studies in patients with mild-to-moderate Alzheimer's disease.

The *first* Phase 3 study is designed to evaluate *disease-modifying* effects of simufilam in Alzheimer's disease. Goal: to demonstrate a slower rate of decline in cognition and health function in subjects treated with simufilam compared to placebo.

The *second* Phase 3 study is designed to evaluate *symptomatic improvement* in Alzheimer's disease. Goal: to demonstrate improved cognition and health function in subjects treated with simufilam compared to placebo.

	Enrollment Target	Treatment	Length of Treatment	Co-Primary	Endpoints	Secondary	Endpoints
				Cognition Scale	Function Scale	Cognition + Function Scale	Dementia-related Behavior Scale
1 st Phase 3	1,000 Subjects	100 mg or 50 mg	18 Months	ADAS-Cog	ADCS-ADL	iADRS	NPI
2 nd Phase 3	600 Subjects	100 mg	9 – 12 Months	ADAS-Cog	ADCS-ADL	iADRS	NPI

We Are On-track to Initiate a Phase 3 Program in 2nd Half 2021.

SavaDx: Our Investigational Diagnostic for Alzheimer's

- The underlying science for simufilam supports the development of a diagnostic technology to detect Alzheimer's disease with a simple blood test, called SavaDx.
- Goal is to detect Alzheimer's disease before the appearance of memory loss.
- SavaDx development plan benefits from long-term scientific & financial support from NIH.



Financials

Eric Schoen - Chief Financial Officer

Unaudited Financials

Nasdaq ticker: SAVA

Shares Outstanding

40.0 million

Insider Ownership: 2.1 million shares

Public Float: 37.9 million shares

Unaudited Financials

Cash Balance @ March 31, 2021:

≈ \$282 million

Debt:

none

Est. Operational Cash Use FY 2021:

≈ \$20 to \$25 million

Intellectual Property

- Simufilam is a novel molecule. We own exclusive, worldwide rights to simufilam and related technologies, without financial obligations to any third party.
- Composition of matter patent protection for simufilam and other novel filamin-binding molecules includes six issued patents and currently runs through 2033.
- There is no patent protection for SavaDx, which is protected by trade secrets, know-how and other proprietary rights technology.

Expected 2021 Milestones

Our Goal is to Initiate a Phase 3 Study of Simufilam in Alzheimer's Disease 2nd Half 2021.

- ✓ End-of-phase 2 meeting with FDA to gain general agreement around a Phase 3 clinical development program in Alzheimer's disease dementia – *completed Jan 2021*
 - ✓ Results of interim analysis (6-month) of open-label study - *completed Feb 2021*
 - ✓ Results of EOP2 meeting with FDA – *completed Feb 2021*
 - ✓ Long-term drug supply agreement with Evonik for simufilam – *completed March 2021*
-
- Oral presentation at AAIC of interim analysis (9-month) of open-label study in Alzheimer's.
 - Results of interim analysis (12-month) of open-label study in Alzheimer's.
 - Manufacture large-scale Phase 3 clinical trial supplies (drug substance + oral tablets).
 - Initiate Cognition Maintenance Study (CMS) June 2021.
 - Complete patient enrollment of on-going, open-label study of simufilam.
 - Publication of Phase 2b results in peer-reviewed technical journal.
 - Results of validation study with SavaDx.

Thank you!



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/](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>