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We Focus on Alzheimer's disease

February 2021 v2.0

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 a 6-month interim analysis 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 and to enter into a long-term commercial drug supply agreement; the timing of validation studies 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.

Drug development and commercialization involve a high degree of risk, and only a small number of research and development programs result in commercialization of a product. Our clinical results from earlier-stage clinical trials may not be indicative of full results or results from later-stage or larger scale clinical trials and do not ensure regulatory approval. You should not place undue reliance on these statements or any scientific data we present or publish.

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This presentation may also contain statistical data and drug information based on independent industry publications or other publicly available information. We have not independently verified the accuracy or completeness of the data contained in these publicly available sources of data and information. Accordingly, we make no representations as to the accuracy or completeness of such data or information. You are cautioned not to give undue weight to such data.

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

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

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Meet the Team

Remi Barbier - Chairman, President & CEO

EXELIXIS® XOMA ARQULE®

Lindsay H. Burns, PhD - SVP Neuroscience

Abgenix elan UNIVERSITY OF CAMBRIDGE

Nadav Friedmann, PhD/MD - CMO, Board member

Eight FDA drug approvals prior to Cassava Sciences.

Johnson & Johnson Abbot Daiichi-Sankyo

Michael Zamloot - SVP Technical Operations

Four FDA drug approvals prior to Cassava Sciences.

Boehringer Ingelheim Ciba-Geigy

Jim Kupiec, MD – Chief Clinical Development Officer

Two FDA drug approvals prior to Cassava Sciences.

Pfizer SANOFI Ciba-Geigy

Eric Schoen - Chief Financial Officer

VERMILLION® PRICEWATERHOUSECOOPERS

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

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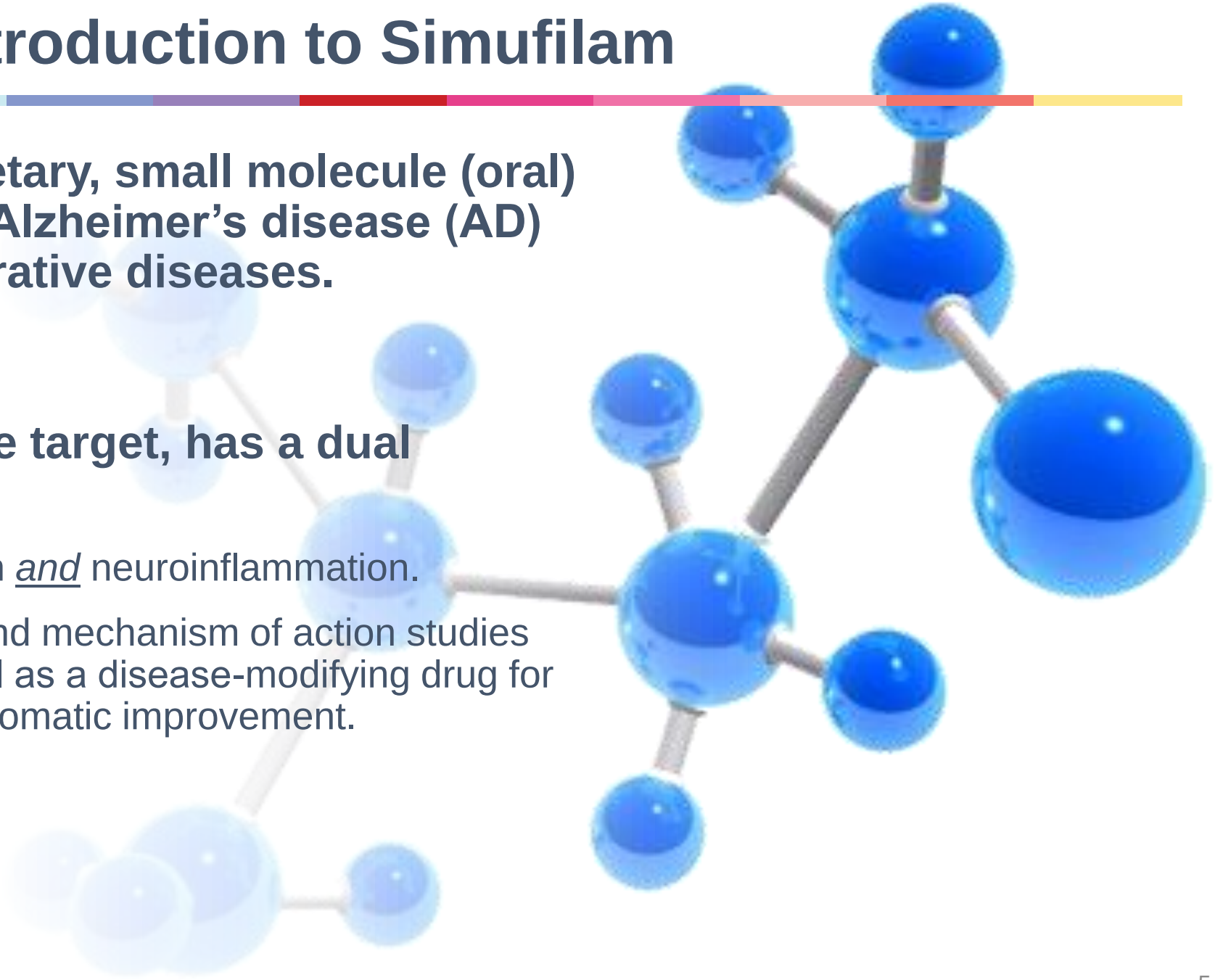
Introduction to Simufilam

- **Simufilam is our proprietary, small molecule (oral) drug candidate to treat Alzheimer's disease (AD) and other neurodegenerative diseases.**

- **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.



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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 double-blind, 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.

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Science & Technology

Lindsay Burns, PhD – SVP Neuroscience

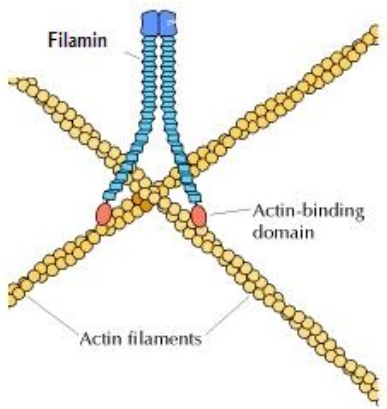
Nadav Friedmann, PhD/MD – Chief Medical Officer

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 <u>enables</u> $A\beta_{42}$ signaling via:

i. **α7-nicotinic acetylcholine receptor (α7nAChR)**
   → hyperphosphorylates tau

ii. **Toll-like receptor 4 (TLR4)**
   → releases inflammatory cytokines

Simufilam binds altered FLNA, restores its proper shape/function, <u>disables</u> $A\beta_{42}$ signaling via α7nAChR and TLR4.

Through a single target, simufilam reduces neurodegeneration and neuroinflammation.

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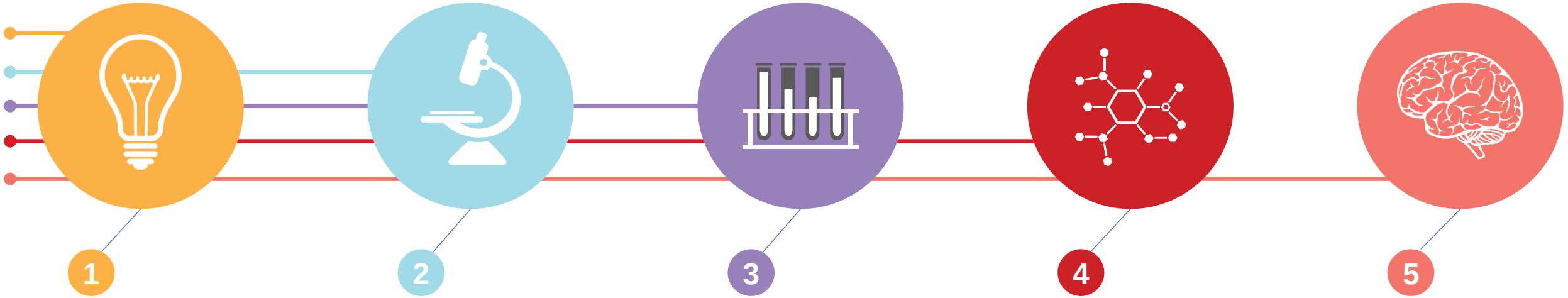
10+ Year In-house Discovery/Development Program



<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
Simufilam (formerly, PTI-125) binds altered FLNA with high affinity, blocks α7nAChR/Aβ interactions. Preclinical testing of simufilam.

2017 - present
IND filing. Clinical testing of simufilam. Positive Phase 2 results reported in Alzheimer's patients.

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Summary of Preclinical Effects

Simufilam	Intracerebro-ventricular (ICV) $A\beta_{42}$ infusion mouse model	Triple transgenic AD mouse model	Post-mortem human AD brain tissue	Post-mortem human age-matched control brain tissue treated with $A\beta_{42}$ in vitro
Reduced FLNA linkage to α7nAChR/TLR4	√	√	√	√
Reduced $A\beta_{42}$ bound to α7nAChR	√	√	√	√
Reduced amyloid deposits and NFTs	√	√		
Reduced tau hyperphosphorylation	√	√		√
Improved function of α7nAChR, NMDAR and insulin receptors	√	√	√	√
Improved synaptic plasticity (activity-dependent Arc expression)		√		√
Reduced inflammatory cytokine levels	√	√		
Improved cognition/behavior		√		

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Clinical Hypothesis

Hypothesis

Simufilam is a disease-modifying drug for Alzheimer's disease that also provides symptomatic improvement.

Phase 2b Study Objective

Evaluate safety, biomarkers and cognition in a randomized, placebo-controlled study of simufilam.

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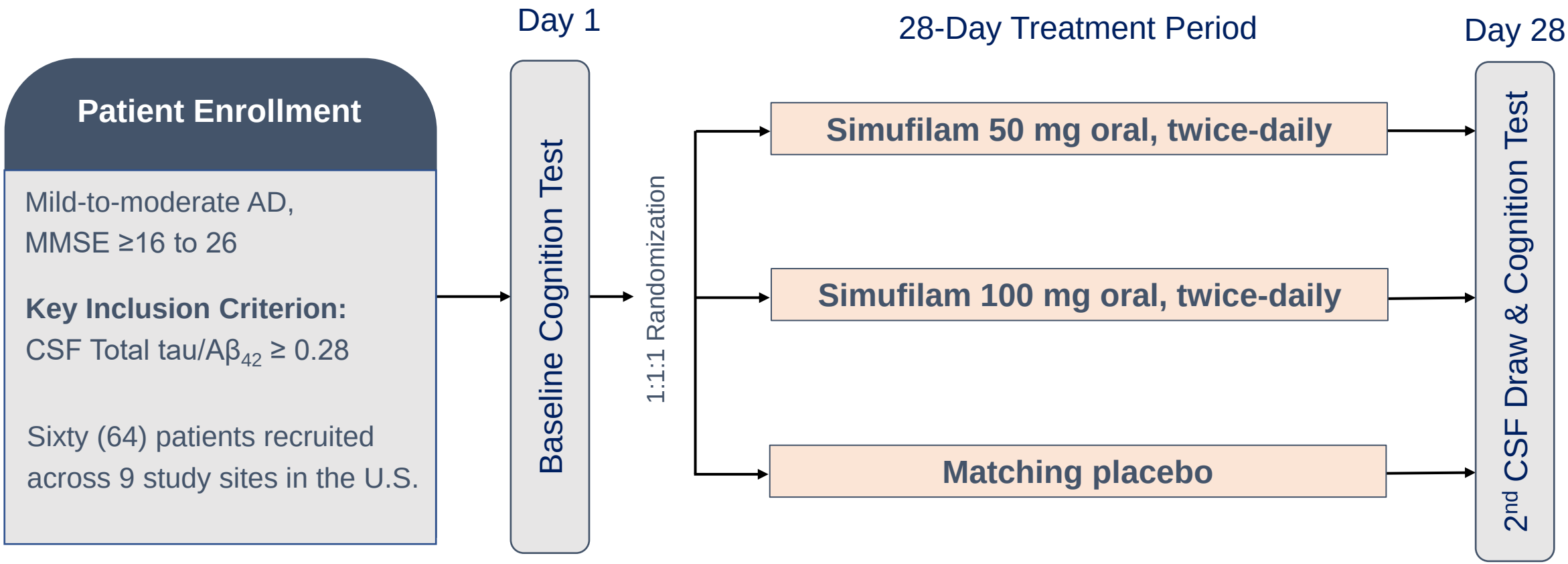
Phase 2b - Study Design

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



Primary Endpoint: **Biomarkers of disease**

Secondary Endpoint: **Cognition**

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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.**

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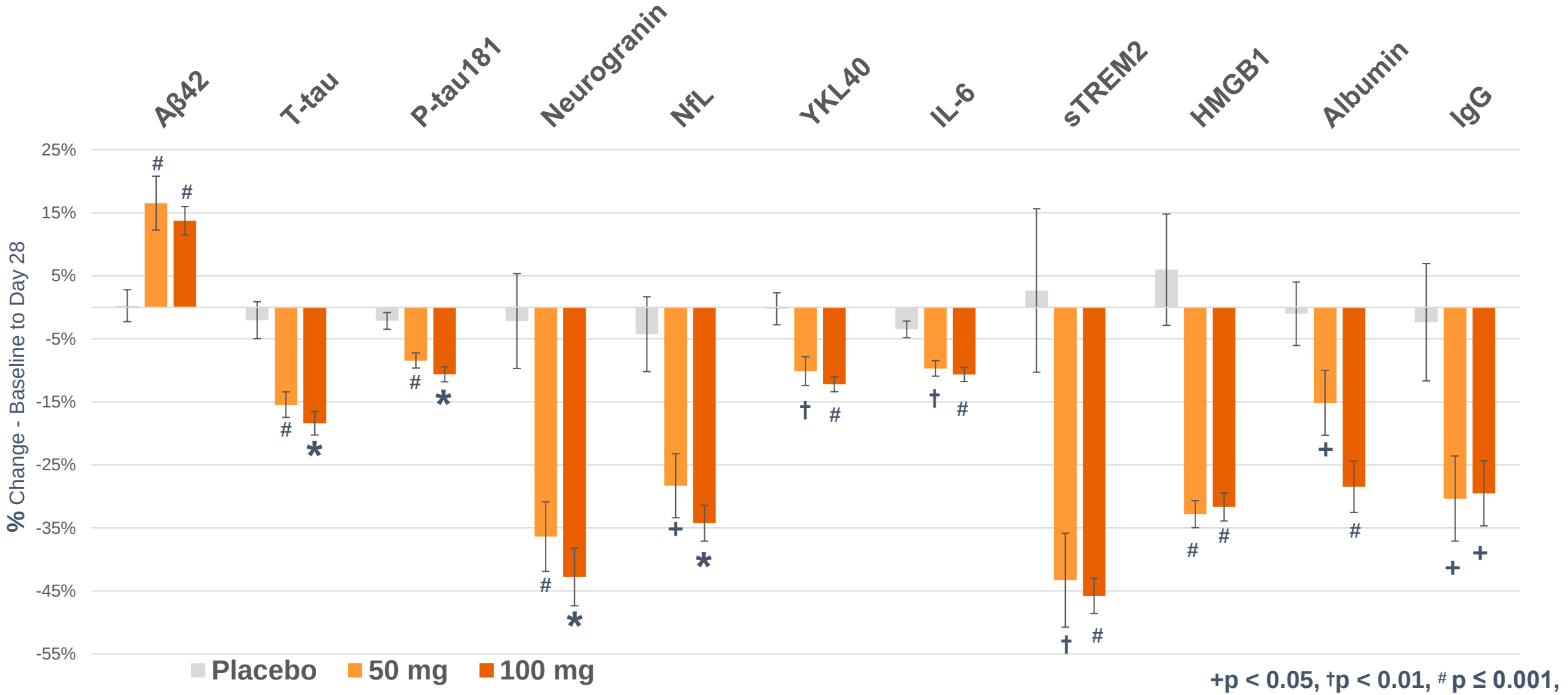
Phase 2b Summary of Results - CSF Biomarkers



+p < 0.05, †p < 0.01, # p ≤ 0.001,
*p < 0.0001 vs. placebo

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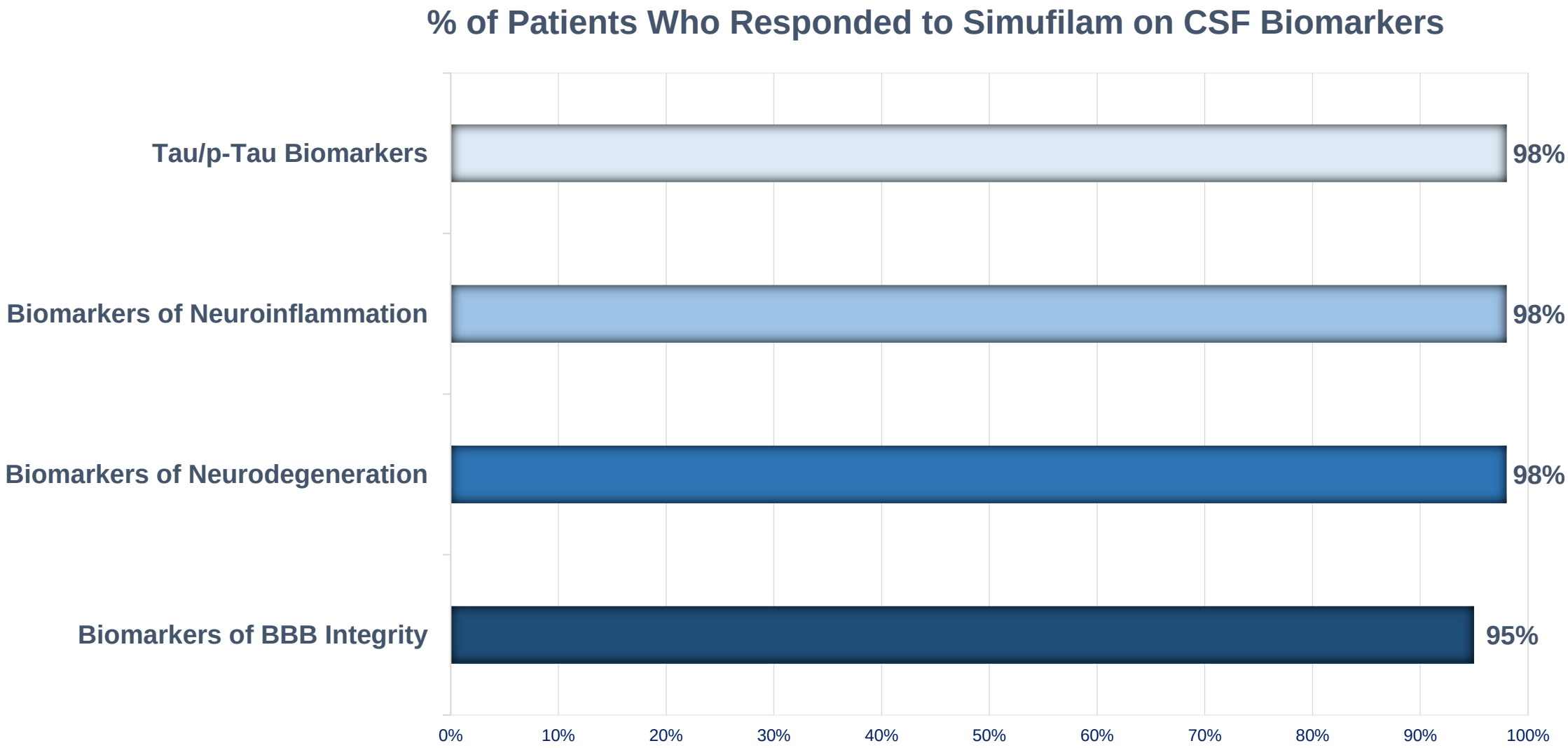
Phase 2b Results – Patient Responder Analysis



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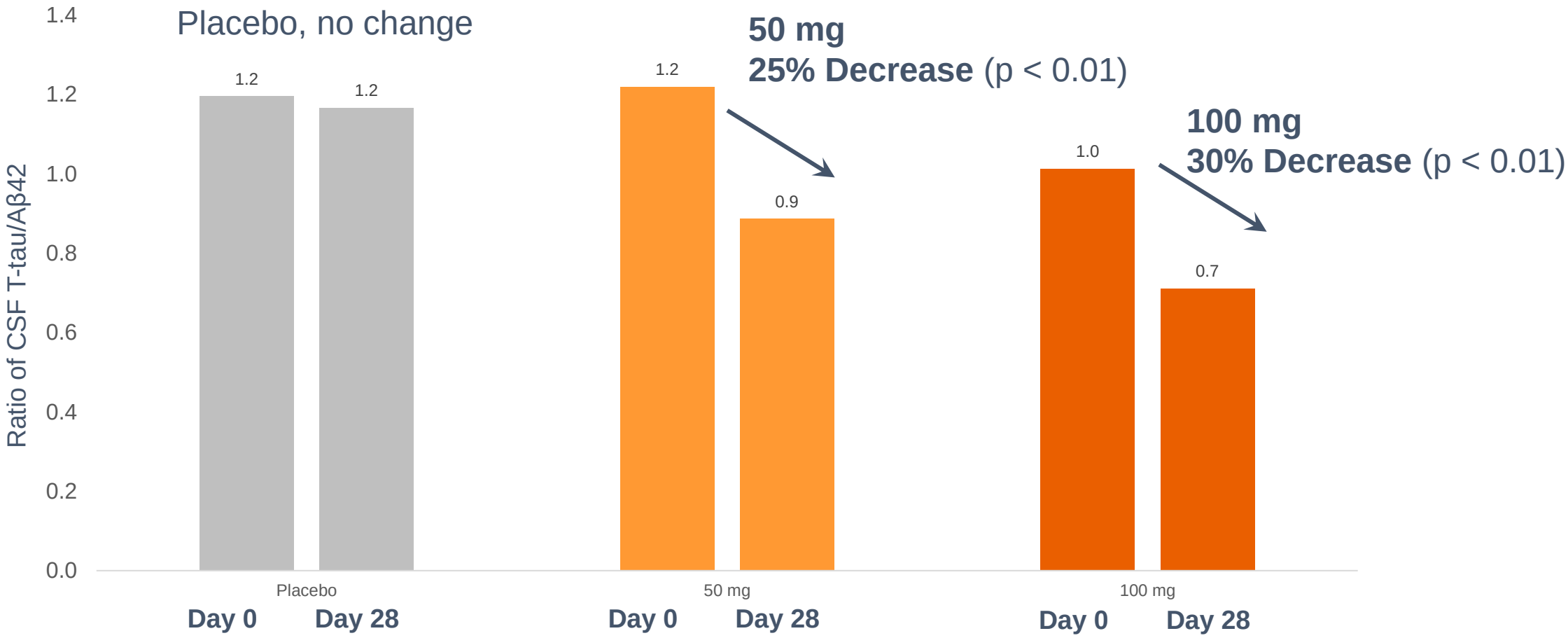
Phase 2b Results - Total tau/Aβ_{42} Decreased Significantly

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

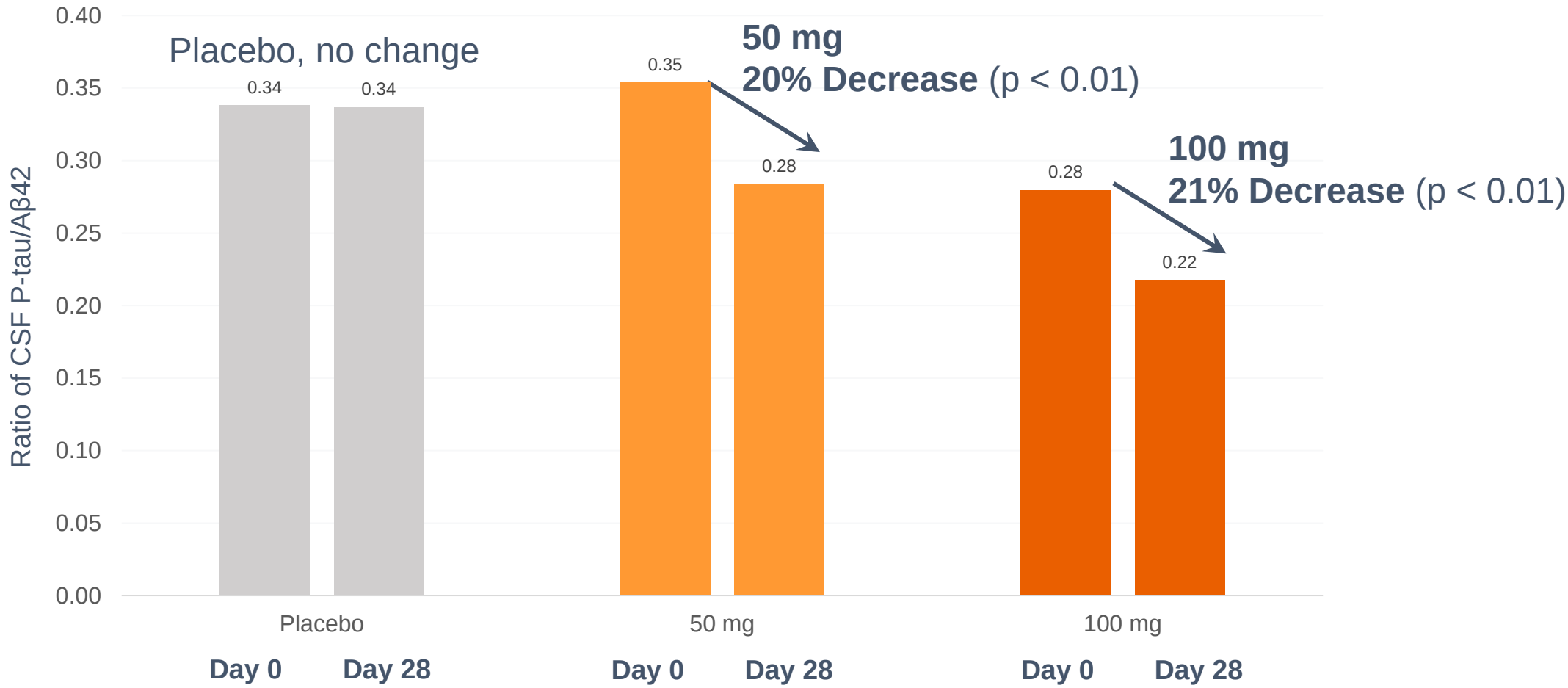
Change in Ratio of CSF T-tau/Aβ_{42} Day 0 to Day 28



Phase 2b Results - P-tau/Aβ$_{42}$ Decreased 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



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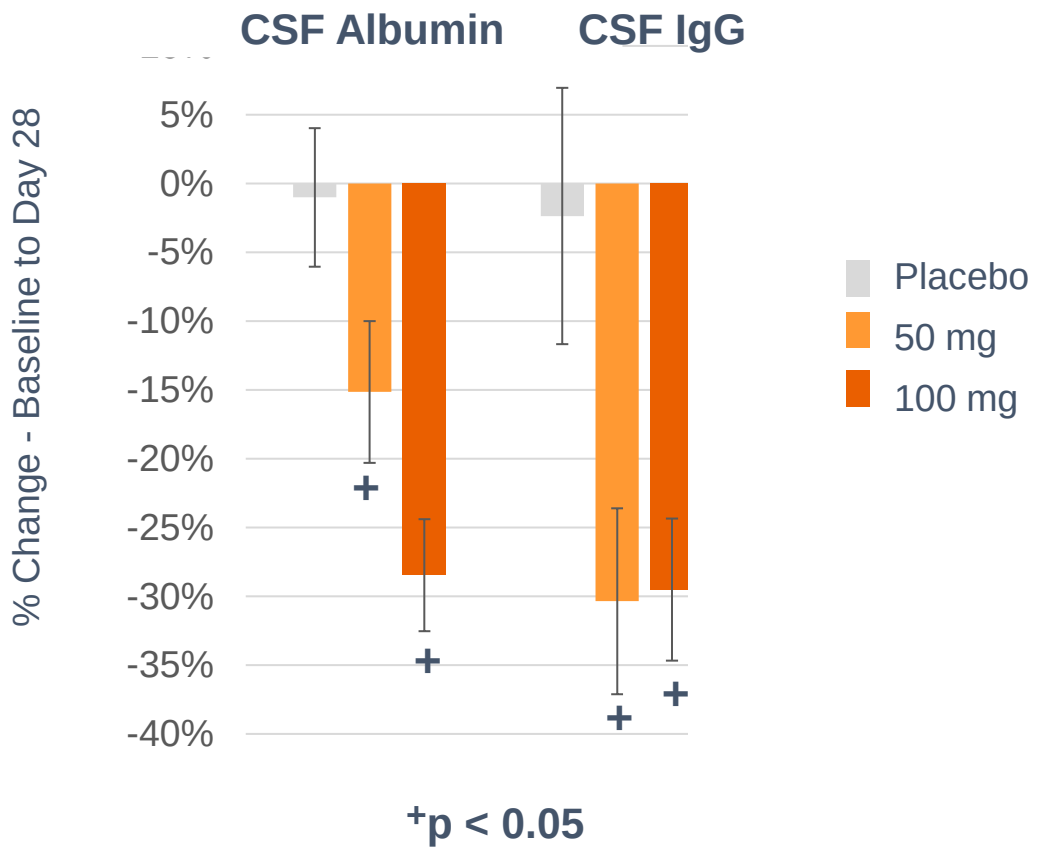
Phase 2b Results – Improved Blood-brain Barrier Integrity



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.*

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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.**

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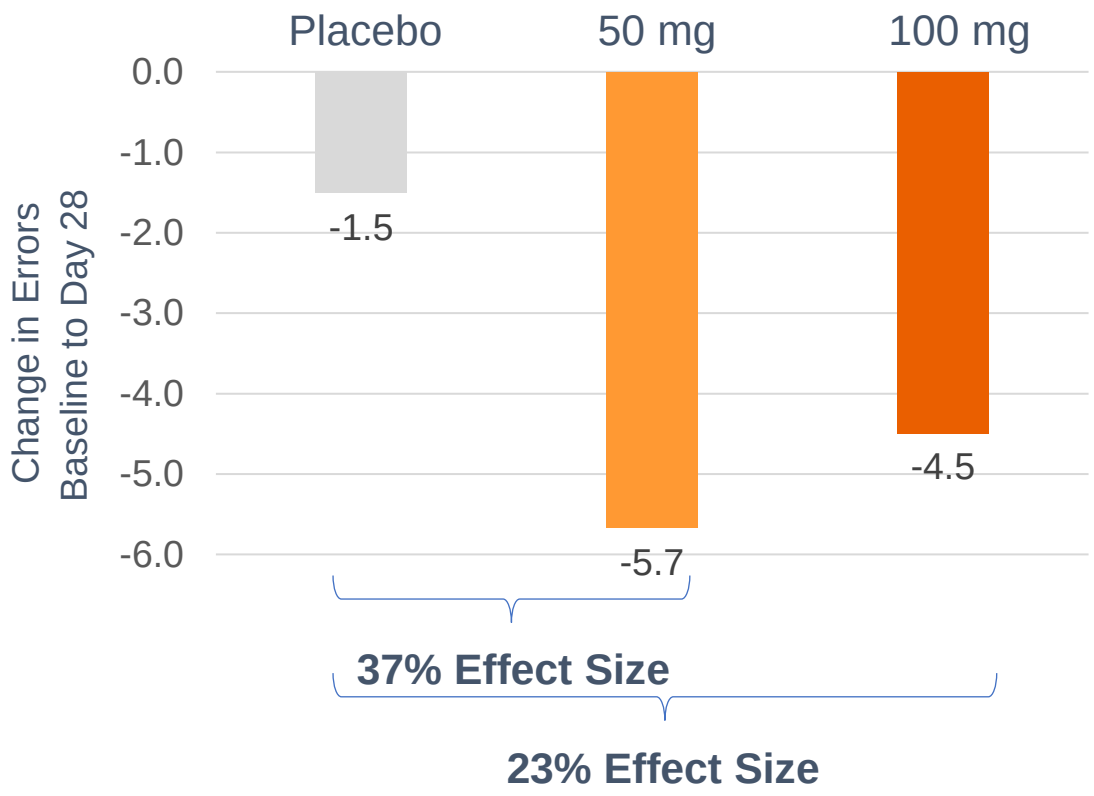
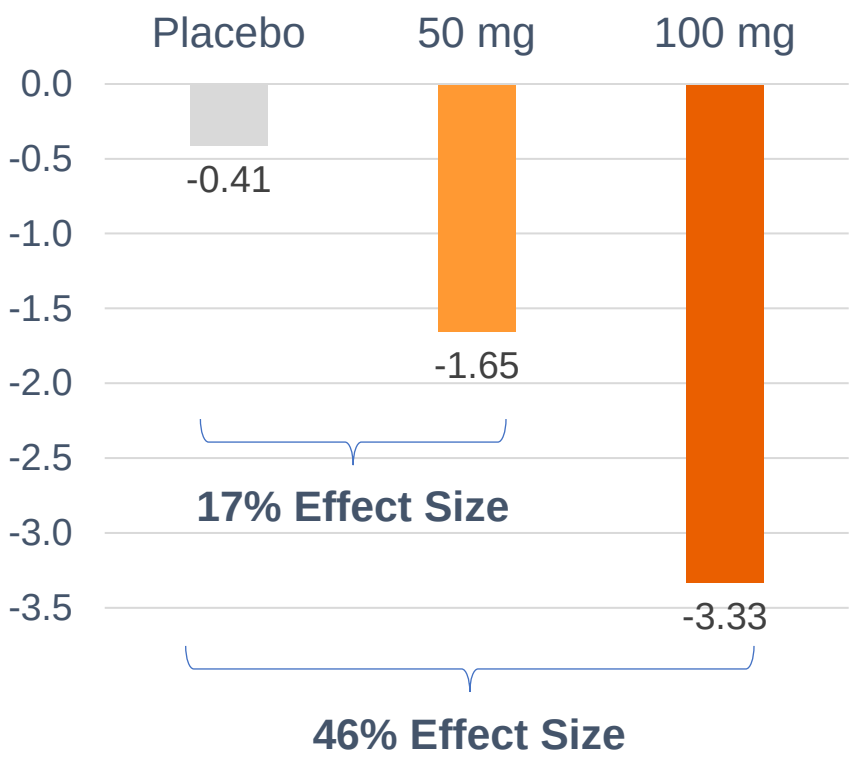
Phase 2b Results – Memory Measurements Improved

Episodic Memory Improved



Spatial Working Memory Improved



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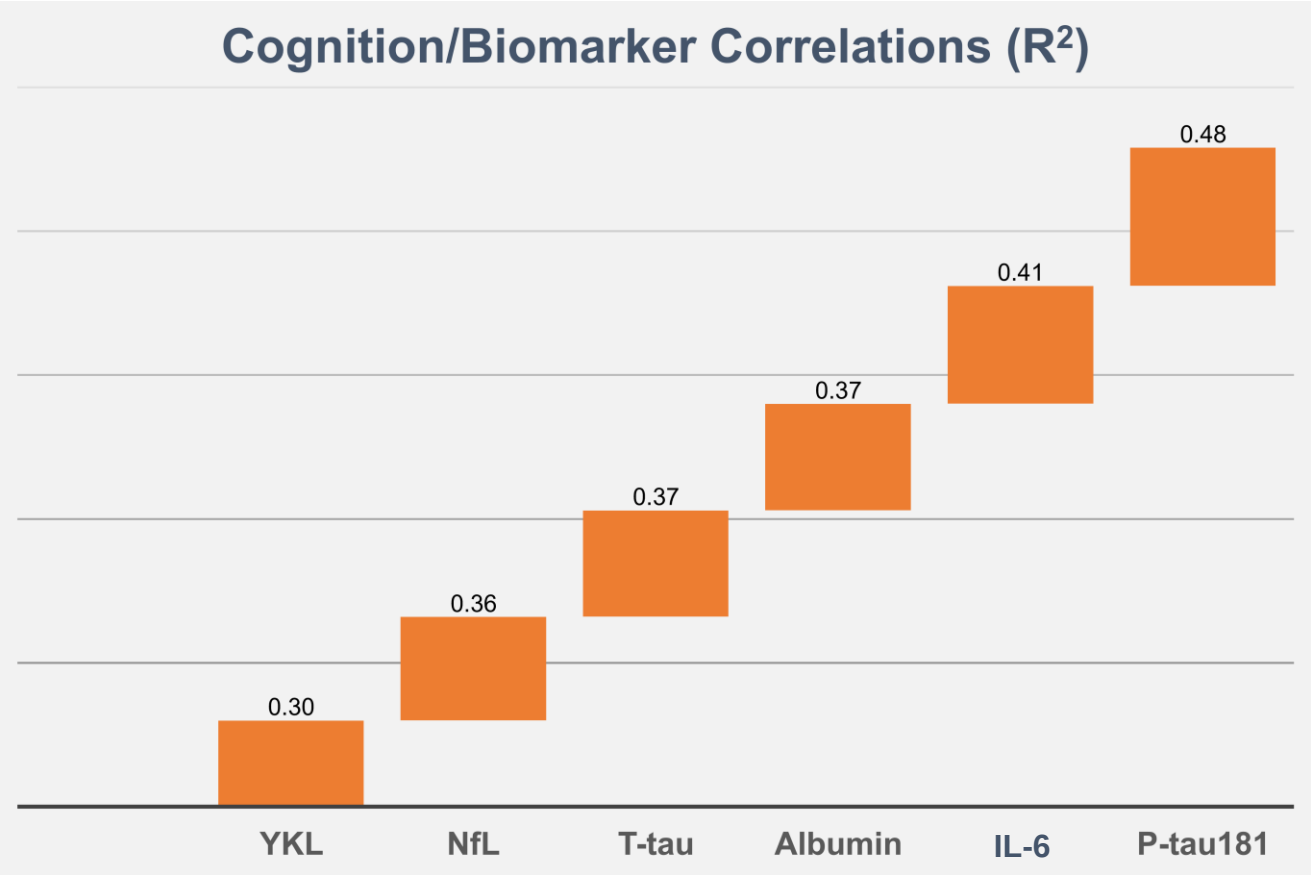
Phase 2b Results - Cognition/Biomarker Correlation

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



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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.**

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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).

- **Total target enrollment is increased, up to 150 patients with mild-to-moderate AD.**

  ≈ 80 patients enrolled as of February 2021.

Interim Analyses planned at 6 and 12 months.

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First Interim Analysis, Open-label Study

- **First interim analysis - first 50 patients who've completed 6 months of treatment.**
- **Simufilam improves 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.

Alzheimer's is a progressive disease. Over time, a patient's cognition will always worsen.

"Experience based on longitudinal studies of ambulatory patients with mild to moderate Alzheimer's disease suggest that scores on ADAS-cog decline by 6 - 12 points per year", according to FDA's Prescription Information sheet for ARICEPT® (donepezil), a drug approved for the treatment of dementia of the Alzheimer's type.

Second interim analysis (12 months) is expected mid-2021.

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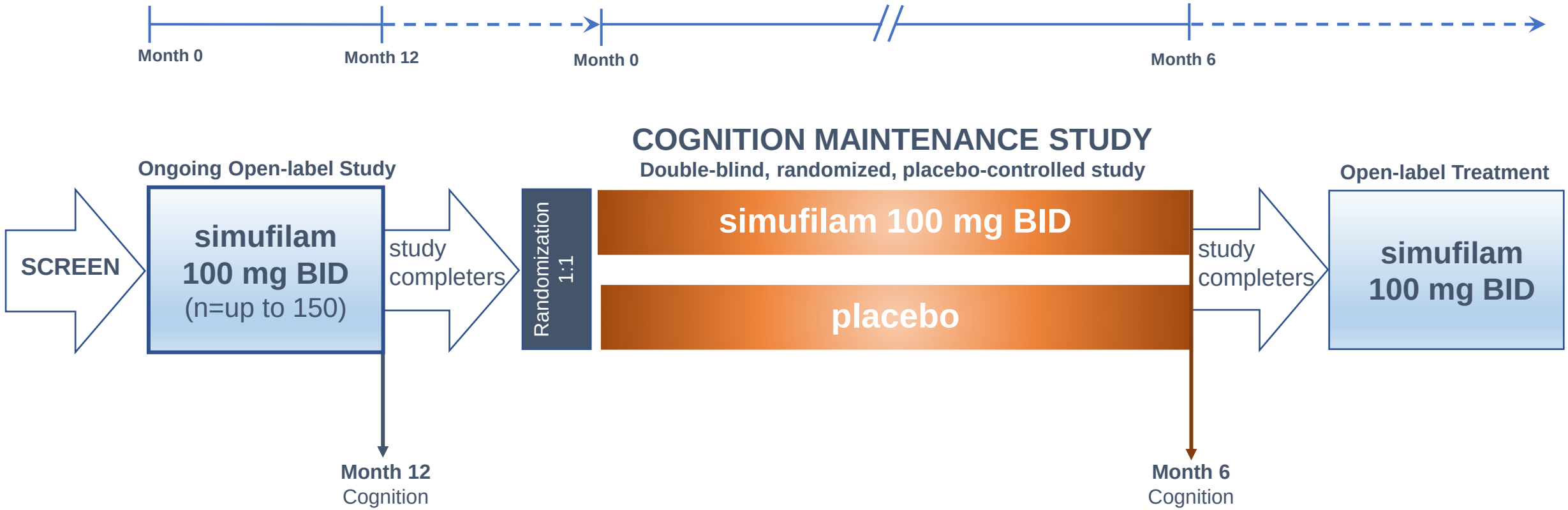
Cognition Maintenance Study (CMS)

CMS is designed to compare cognition in AD patients who've completed the open-label study and then continue vs. discontinue simufilam.



CMS initiation is expected mid-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.

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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.

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

We are on-track to initiate the Phase 3 program in the 2nd half 2021.

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ADAS-Cog = The Alzheimer's Disease Assessment Scale – Cognitive Subscale, a measure of cognition
ADCS-ADL = Alzheimer's Disease Cooperative Study – Activities of Daily Living, a measure of health function
iADRS = integrated Alzheimer's Disease Rating Scale, a composite measure of cognition and health function
NPI = Neuropsychiatric Inventory

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.

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Financials

Eric Schoen - Chief Financial Officer

Unaudited Financials

Nasdaq ticker: SAVA	
Shares Outstanding	**39.9 million[1]**
Insider Ownership:	*2.1 million shares*
Public Float:	*37.8 million shares*

Unaudited Financials	
Cash Balance @ February 12, 2021:	**≈ $280 million[1]**
Debt:	***none***
Est. Cash Use Full-year 2021:	**≈ $20 to $25 million**

Footnote 1: Unaudited cash balance includes net proceeds of $189.7 million received from the sale of 4.1 million common shares in an offering completed February 12, 2021.

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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.**

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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 (EOP2) 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***

- **Results of interim analysis (12-month) of ongoing open-label study in Alzheimer's.**
- **Long-term supply agreement with contract manufacturer for simufilam.**
- **Manufacture large-scale Phase 3 clinical trial supplies (drug substance + oral tablets).**
- **Initiate Cognition Maintenance Study (CMS) mid-2021.**
- **Complete patient enrollment of on-going, open-label study of simufilam.**
- **Publication of Phase 2b results in peer-reviewed technical journal.**
- **Initiate validation study with SavaDx.**

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Thank you!

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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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