



We Focus on Alzheimer's disease

April 2022

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, that may include but are not limited to: our strategy and plans; the size and scope of our pivotal Phase 3 trial and its likelihood of success; the interpretation of clinical data generated in interim analyses of an open-label study, plans to announce full study results and the timing thereof; plans to conduct ad hoc interim analyses on open-label clinical data and the timing thereof; the initiation and progression of a scientific inquiry undertaken by CUNY and the publication of its results; the restoration of scientific reputations; the treatment of Alzheimer's disease; the status of current and future clinical studies with simufilam; the efficacy of simufilam in humans; the publication of an analysis regarding the expected rate of cognitive decline in people with Alzheimer's disease; our ability to expand therapeutic indications for simufilam outside of Alzheimer's disease; the development path for SavaDx and the use of alternative methods of detection; expected cash use in future periods; clinical data presented at the 2021 Alzheimer's Association International Conference (AAIC), including a subsequent erratum regarding visual errors not caught in proofing; a technical paper published in 2017 in Neurobiology of Aging and a subsequent erratum regarding a visual error not caught in proofing; 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 regulatory approval and subsequent 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.

Such statements are based 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, potential health benefits, if any, of changes in levels of biomarkers, the severity and duration of health care precautions given the COVID-19 pandemic, any unanticipated impacts of the pandemic on our business operations, including those described in the section entitled "Risk Factors" in our Annual Report on Form 10-K for the year ended December 31, 2021 and future reports to be filed with the SEC. The foregoing sets forth many, but not all, of the factors that could cause actual results to differ from expectations in any forward-looking statement. In light of these risks, uncertainties and assumptions, the forward-looking statements and events discussed in this presentation are inherently uncertain and may not occur, and actual results could differ materially and adversely from those anticipated or implied in the forward-looking statements. Accordingly, you should not rely upon forward-looking statements as predictions of future events. Except as required by law, we disclaim any intention or responsibility for updating or revising any forward-looking statements contained in this presentation. For further information regarding these and other risks related to our business, investors should consult our filings with the SEC, which are available on the SEC's website at www.sec.gov.

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 represent the official views of the National Institutes of Health (NIH).

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 and Robertson Stephens & Company



Richard Barry

Founding Partner,
Portfolio Manager,
Eastbourne Capital



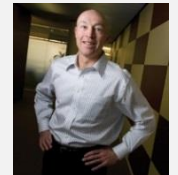
Robert Gussin, PhD

Formerly, CSO & Corporate VP, Science
and Technology, Johnson & Johnson



Patrick Scannon, MD/PhD

Formerly, Founder & CSO/CMO -
XOMA Corporation



Michael O'Donnell

Partner, Orrick LLP

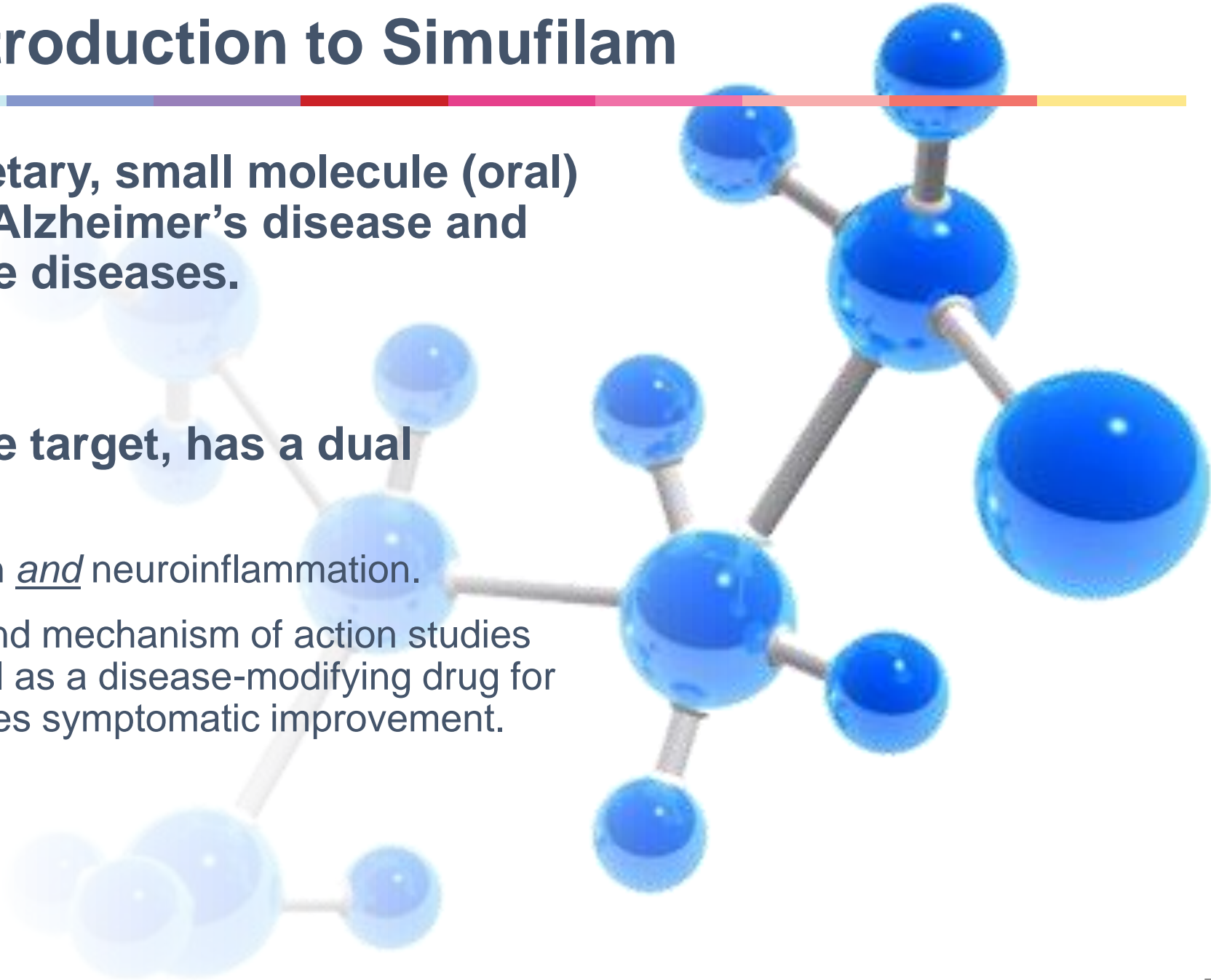
Cassava Sciences Highlights

Our goal is to defeat Alzheimer's disease.

- We are developing simufilam for the proposed treatment of Alzheimer's disease.
- Simufilam is a proprietary, oral drug candidate, developed in-house with academic collaborators.
- We are now conducting Phase 3 studies with simufilam in patients with mild to moderate Alzheimer's.
- More than 6 million Americans are living with Alzheimer's disease and this number may rise to nearly 13 million by 2050, according to the Alzheimer's Association.
- Our scientific approach is unique, our clinical data is highly differentiated.
- Science programs developed with support from the National Institutes of Health (NIH).

Introduction to Simufilam

- Simufilam is our proprietary, small molecule (oral) drug candidate to treat Alzheimer's disease 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 Alzheimer's that also provides symptomatic improvement.



Clinical/Regulatory Development of Simufilam

Completed

- ✓ *2017: Phase 1 dose-escalating safety study in human volunteers.*
- ✓ *2019: Phase 2a open-label safety study in Alzheimer's patients.*
- ✓ *2020: Phase 2b randomized, placebo-controlled study in Alzheimer's patients.*
- ✓ *2021: Interim analysis of open-label study in first 50 patients to complete 6, 9 & 12 months of treatment.*
- ✓ *2021: End-of-Phase 2 meeting with FDA.*
- ✓ *2021: Two FDA Special Protocol Assessments for on-going Phase 3 studies.*

On-going

- ☐ *Two Phase 3 studies in Alzheimer's patients.*
- ☐ *Open-label study in Alzheimer's patients.*
- ☐ *Randomized, placebo-controlled Cognition Maintenance Study (CMS) in Alzheimer's patients.*

Clinical Snapshot – Q1 2022

On-going Studies in Alzheimer's disease

Phase 3 Program

☐ *Two Phase 3 studies in Alzheimer's patients.*

- ✓ 60 subjects are now enrolled in the Phase 3 program, split almost equally among the two studies.
- ✓ Over 105 clinical trial sites across the U.S. and Canada are now recruiting patients, with many sites activated in Q1 2022.
- ✓ Our Phase 3 studies have a relatively long & rigorous screening process to ensure only qualified patients who meet all inclusion & exclusion criteria are successfully enrolled. Approximately 170 patients are currently in screening.

Our goal is to activate a total of 175 or more clinical trial sites for the Phase 3 program, including sites outside of North America.

Other Clinical Studies

☐ *Open-label study in Alzheimer's patients.*

- ✓ The open-label study is fully-enrolled (over 200 subjects).
- ✓ We expect all subjects will have completed drug treatment in \approx 6 months.

Our goal is to complete the open-label study 2nd half 2022 and to announce data by year-end 2022.

☐ *Randomized, placebo-controlled Cognition Maintenance Study (CMS) in Alzheimer's patients.*

- ✓ CMS study is 69% enrolled towards a target enrollment of \approx 100 subjects.
- ✓ All clinical data remains blinded.

Our goal is to complete enrollment for the CMS study 2nd half 2022 and to announce data in 2023.

Science & Technology

Lindsay Burns, PhD – SVP Neuroscience

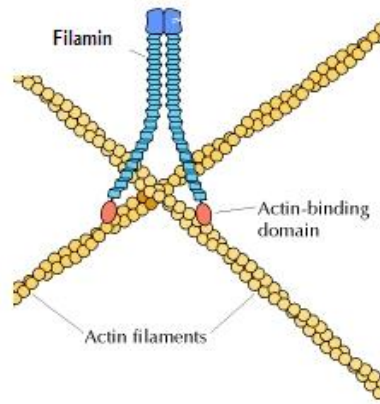
Nadav Friedmann, PhD/MD – Chief Medical Officer

Jim Kupiec, MD - Chief Clinical Development Officer

Proposed 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.

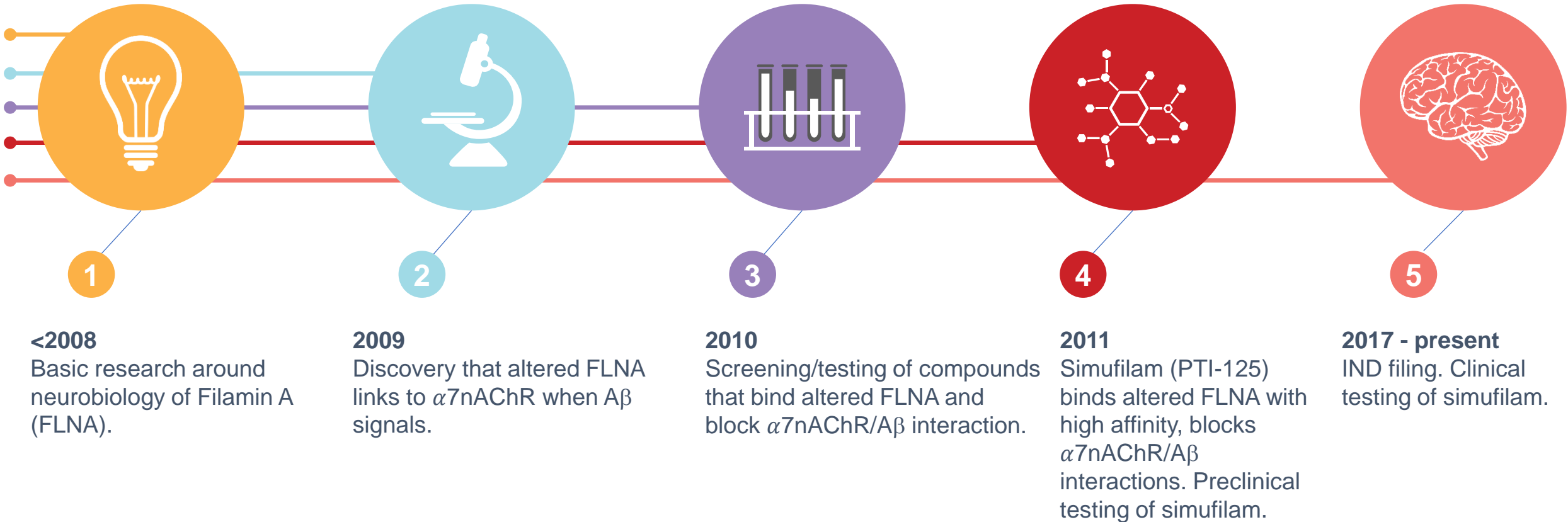
Altered FLNA enables $A\beta_{42}$ signaling via:

- i. $\alpha 7$ -nicotinic acetylcholine receptor ($\alpha 7nAChR$)
→ 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 $\alpha 7nAChR$ and TLR4.

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

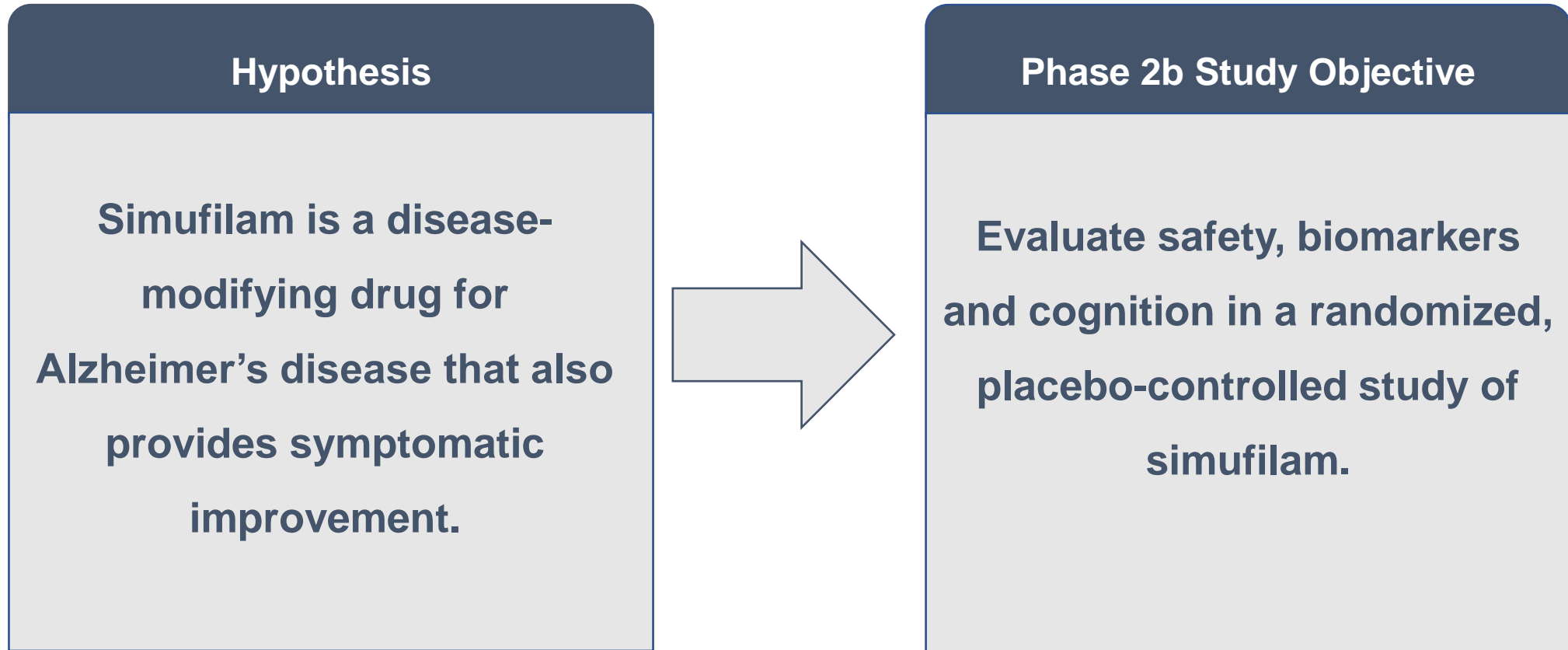
10+ Year In-house Discovery/Development Program



Summary of Preclinical Effects

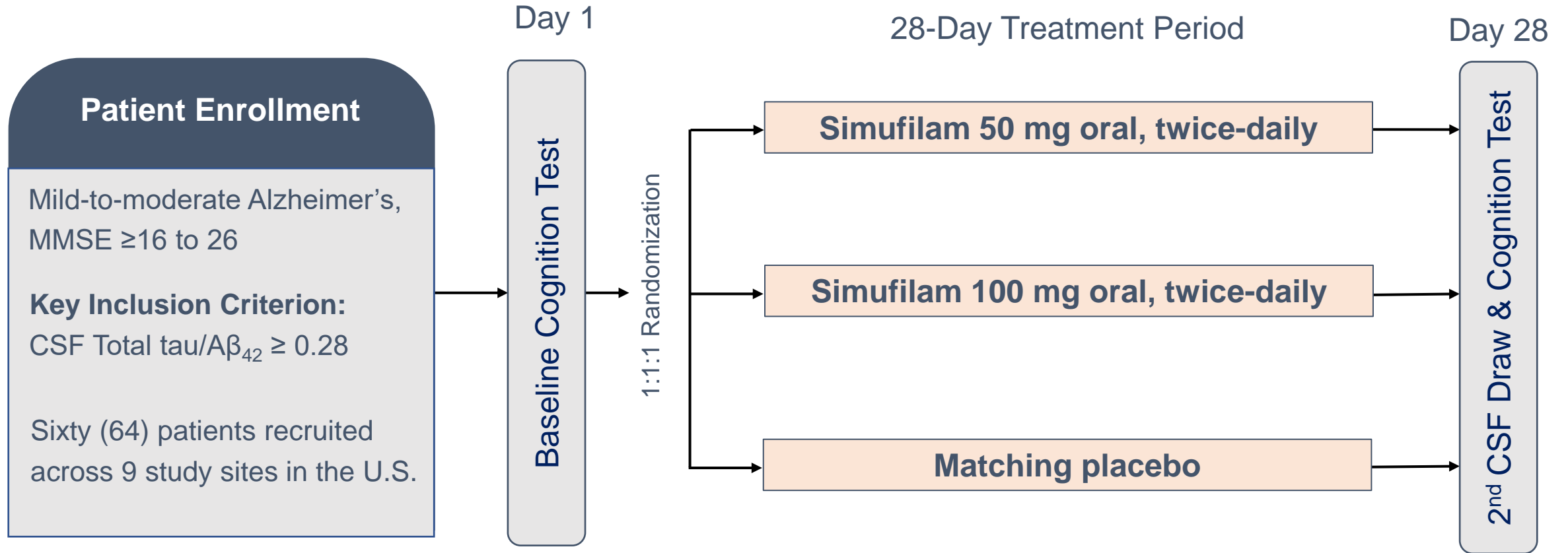
Simufilam	Intracerebro-ventricular (ICV) Aβ_{42} infusion mouse model	Triple transgenic AD mouse model	Post-mortem human AD brain tissue	Post-mortem human age-matched control brain tissue treated with Aβ_{42} in vitro
Reduced FLNA linkage to $\alpha 7$ nAChR/TLR4	√	√	√	√
Reduced A β_{42} bound to $\alpha 7$ 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

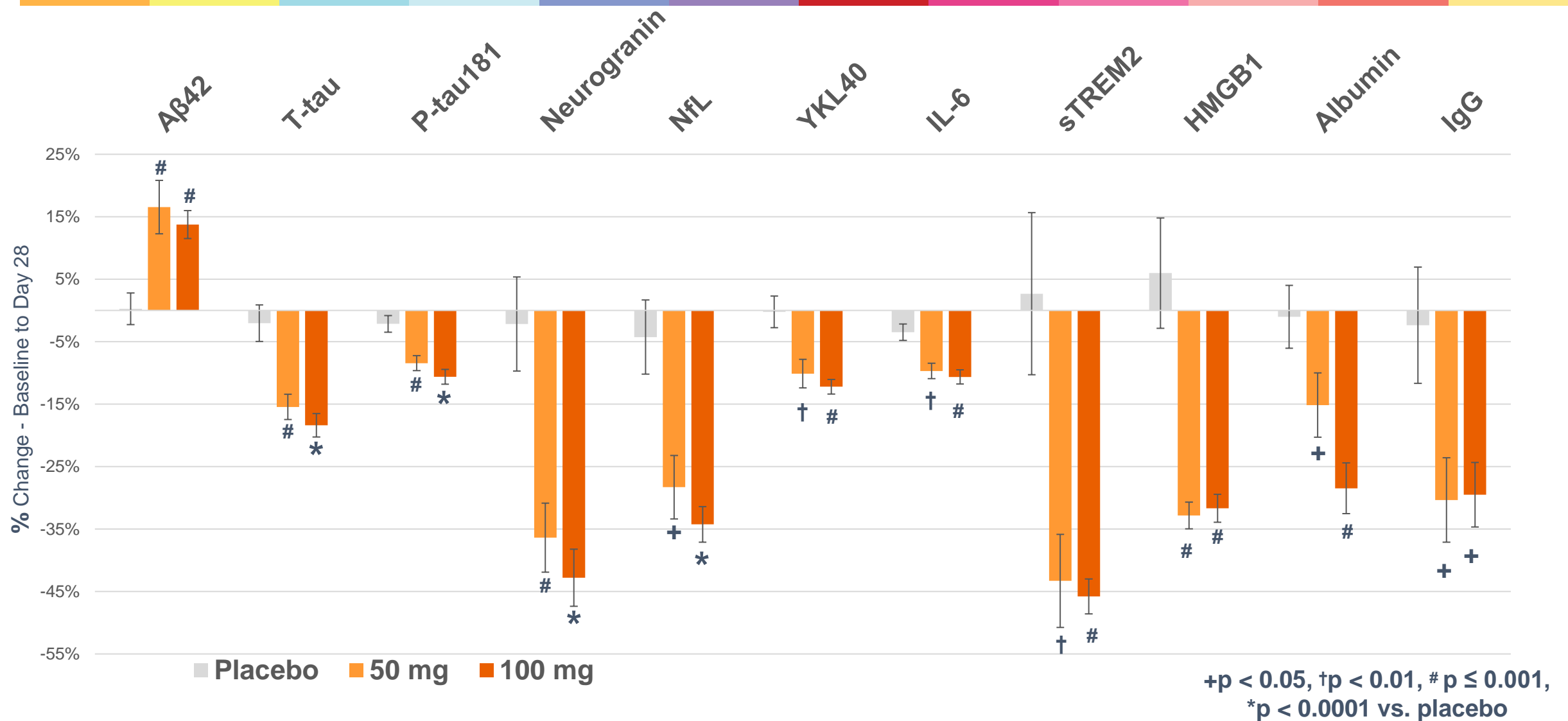
Double-blind, Randomized, Placebo-controlled, Multi-center, Safety Study



Phase 2b Results – Safety & Baseline

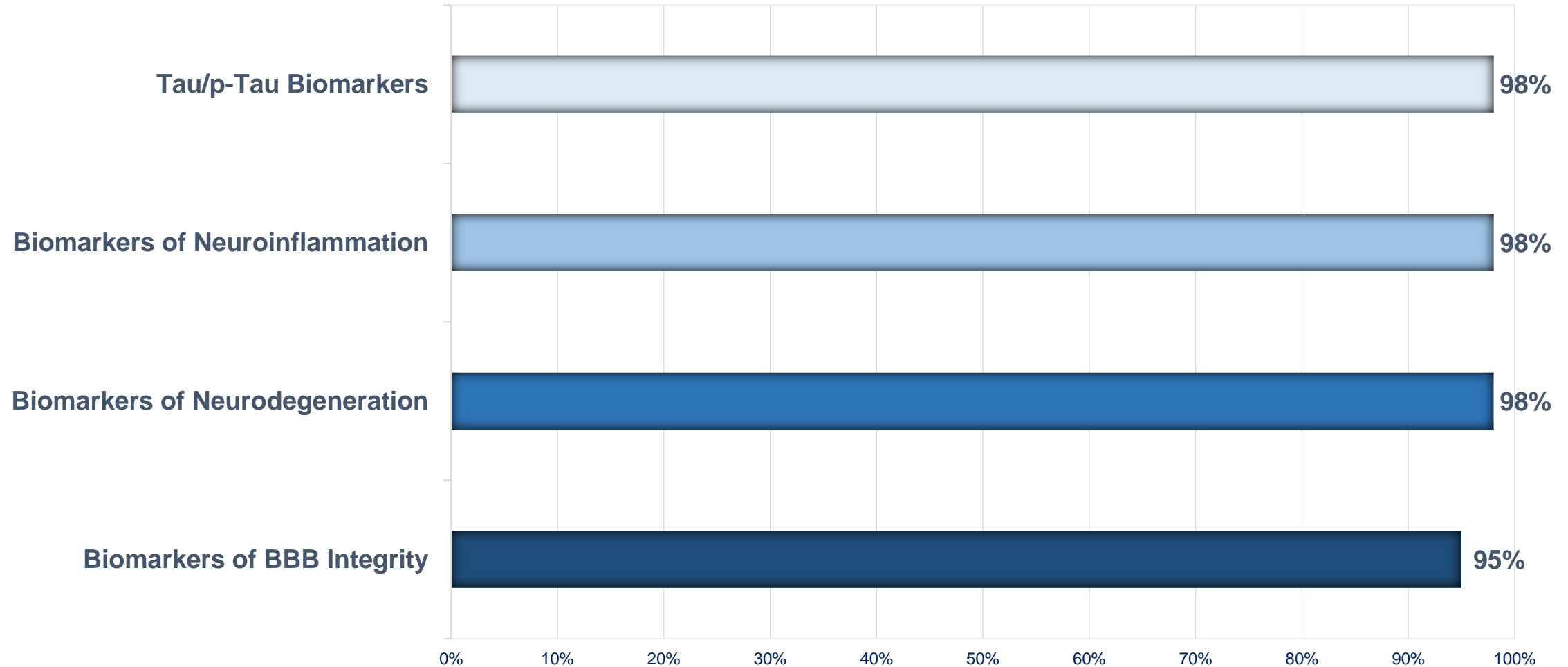
- **Simufilam was safe and well-tolerated**
- **No serious adverse events**
- **No drug-related patient discontinuation**
- **No drug-related adverse events**
 - Common, non-persistent side-effects observed in placebo & drug groups
- **Baseline characteristics were well-balanced between treatment groups, 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 Study Conclusions

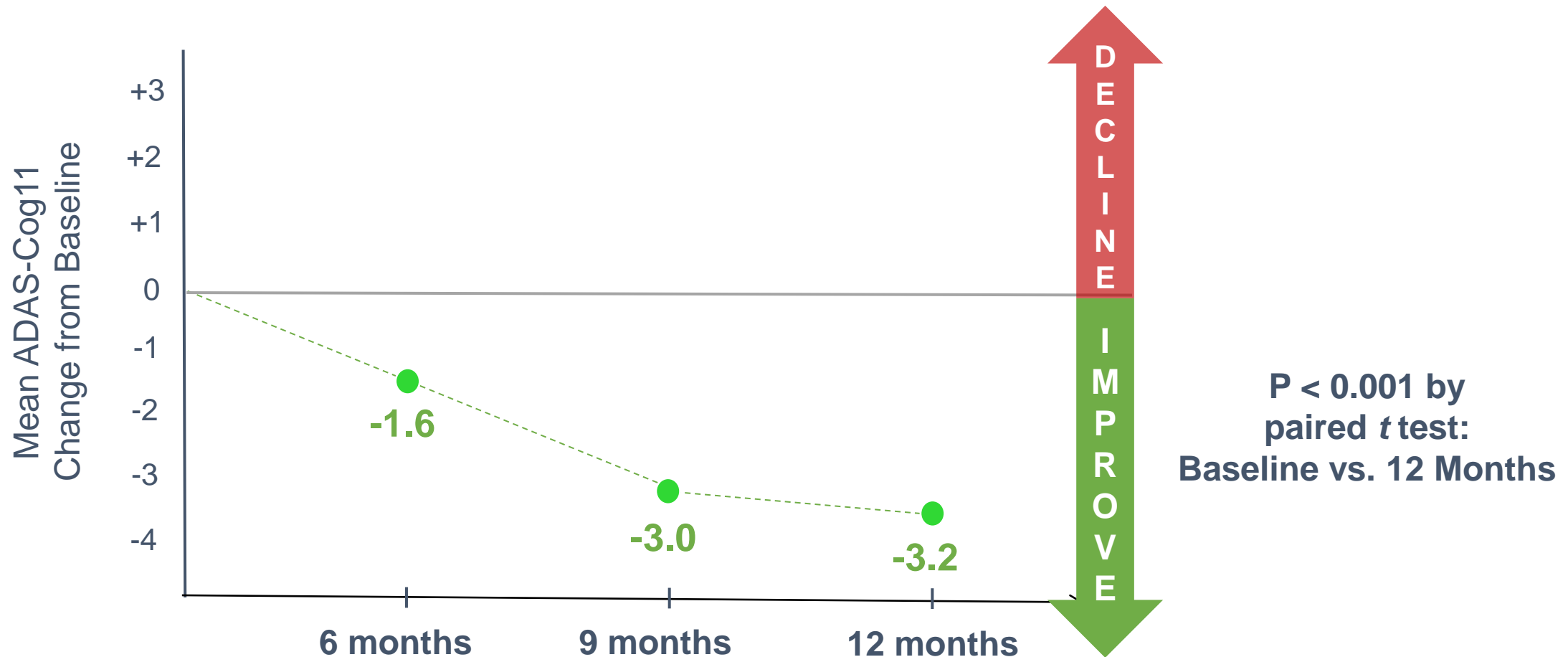
- Simufilam showed promising treatment effects in a double-blind, randomized, placebo-controlled study in patients with mild-to-moderate Alzheimer's disease.
- Simufilam improved a panel of validated biomarkers of disease pathology, neuroinflammation and integrity of the blood-brain barrier.
- Evidence of simufilam's safety and efficacy in Alzheimer's disease still needs to be established by FDA statutory requirements.
 - Phase 3 studies are on-going with simufilam in patients with Alzheimer's disease.

Ongoing Open-label Study

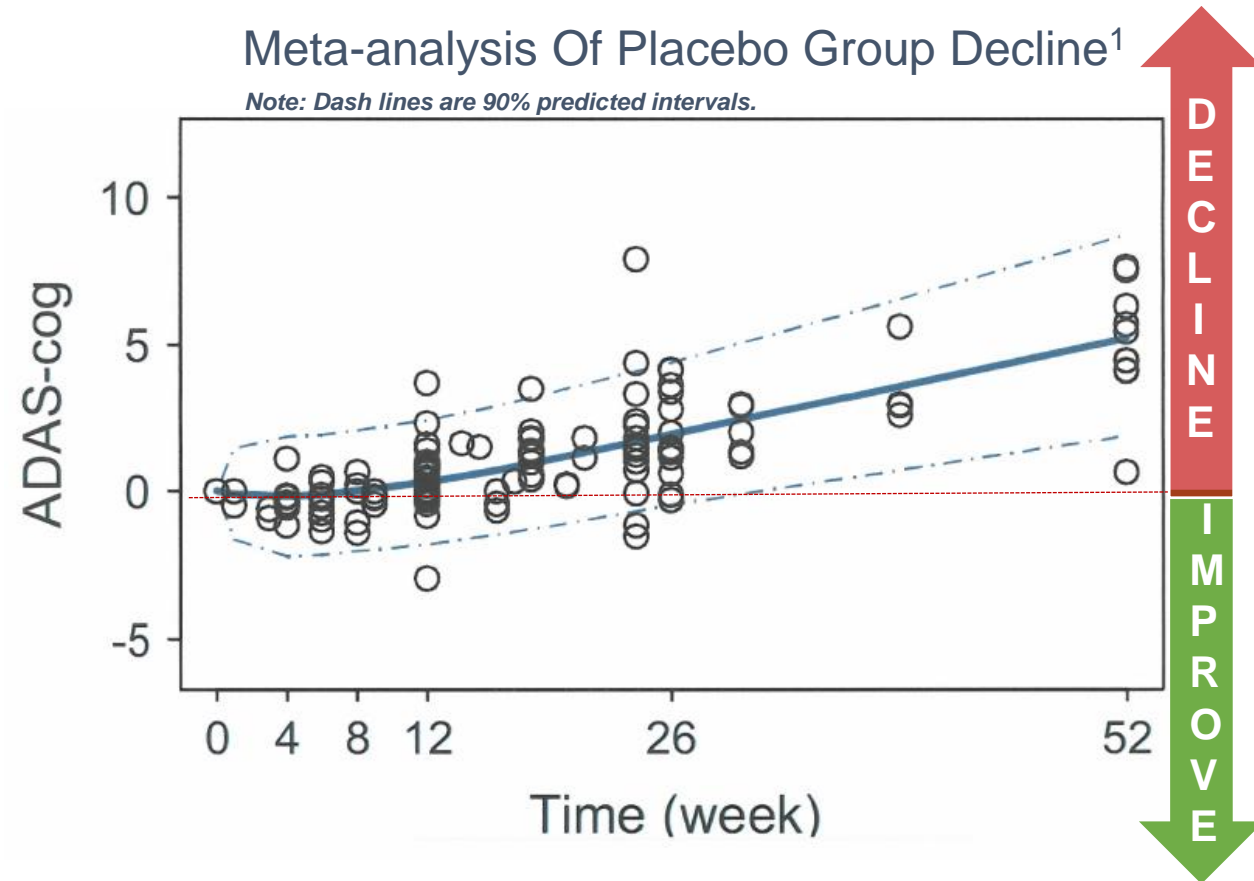
- **We are conducting a one-year, open-label safety study of simufilam, with scientific and financial support from the National Institutes of Health (NIH).**
- **Study subjects have mild-to-moderate Alzheimer's disease (MMSE 16 to 26) and are evaluated for safety, cognition and behavior.**
 - Study is fully enrolled: \approx 200+ study subjects from 16 investigator sites in the U.S. and Canada.
 - Simufilam appears safe and well-tolerated.
- **In 2021, we announced top-line safety & cognitive results of the first 50 study subjects who completed 6, 9 & 12 months of open-label treatment with simufilam 100 mg b.i.d.**
 - Treatment effects observed in an open-label study are not proof of drug safety or efficacy, nor can open-label data predict clinical success in a Phase 3 program.

Open-label Study – Cognition

Change in cognition scores observed in first 50 study subjects who completed 6, 9 & 12 months of open-label treatment with simufilam 100 mg b.i.d.

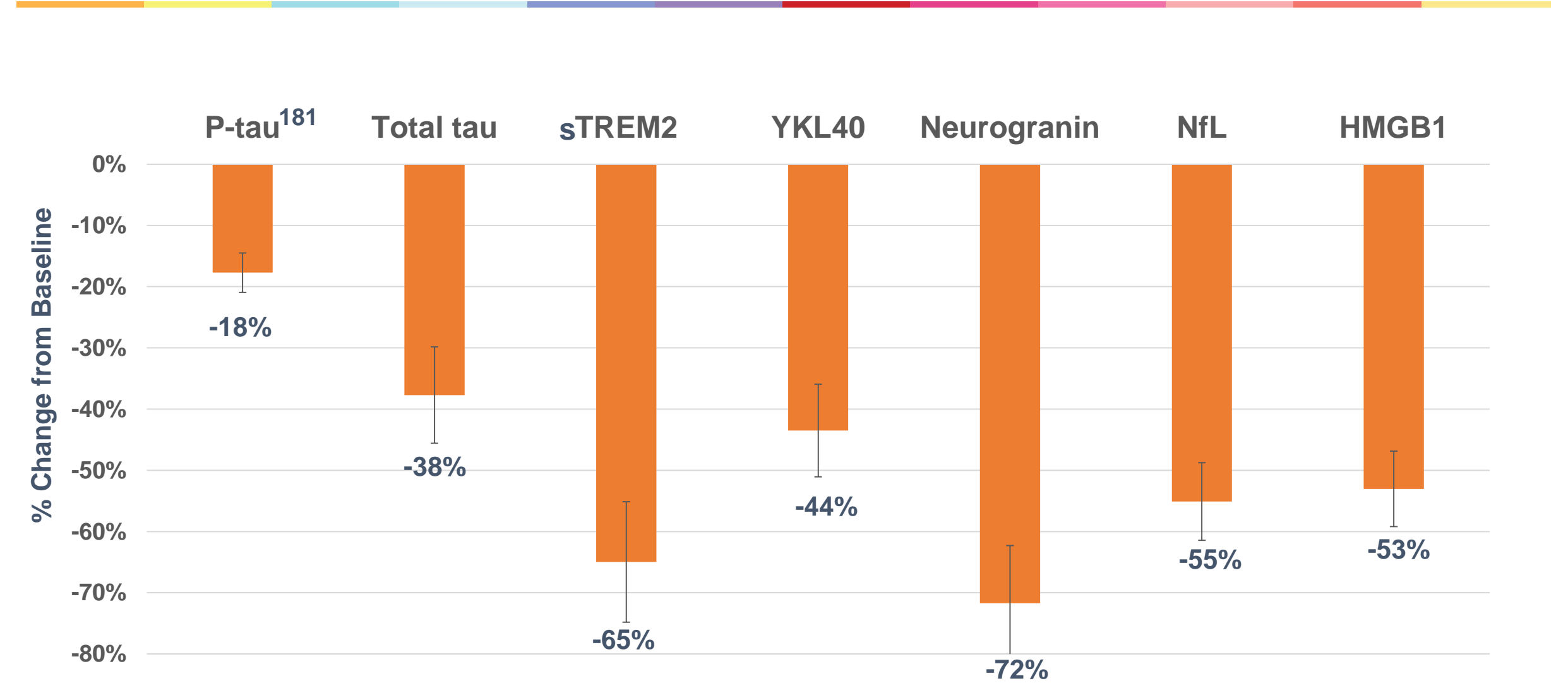


Expected Rate of Cognitive Decline in AD - Literature



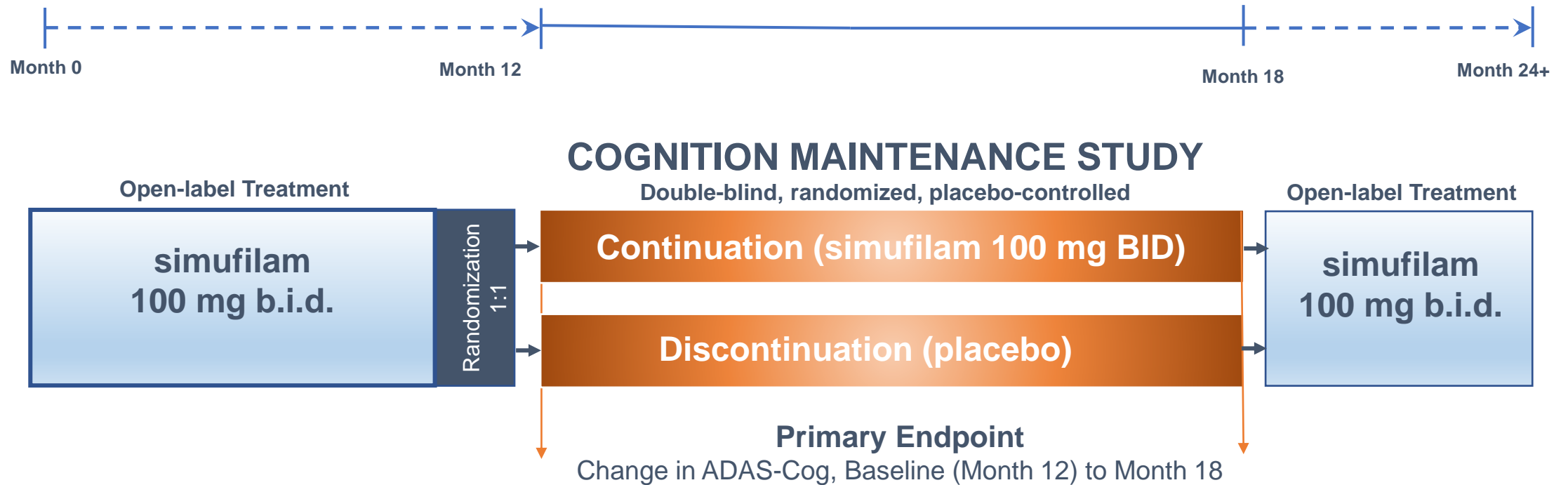
- Cognitive decline was reported in a published, meta-analysis of 20,000 patients with mild-to-moderate AD in randomized, controlled trials¹. **5.5 point average decline over 12 months on ADAS-Cog among study subjects who were administered placebo in randomized, controlled trials.**
- Cognitive decline was reported in two P3 studies of Biogen's aducanumab in patients with early AD²: **5.2 point average decline over 18 months on ADAS-Cog among study subjects who were administered placebo in randomized, controlled trials.**

Open-label Study - CSF Biomarkers at 6 Months (N=25)



Cognition Maintenance Study (CMS)

Goal is to compare cognition in ≈ 100 AD patients who continue vs. discontinue simufilam following 1-year open-label treatment.



CMS was initiated May 2021. As of April 2022, 69 subjects have now been enrolled.

Regulatory Strategy

- **Successful End-of-phase 2 (EOP2) meeting was held with FDA January 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.
 - FDA agrees that the completed Phase 2 program, together with well-defined Phase 3 clinical program, are sufficient to show evidence of clinical efficacy.
 - Agreement on use of co-primary efficacy endpoints to assess treatment benefits.
- **Agreement reached with FDA on two Special Protocol Assessments for Phase 3.**

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 (MMSE 16 to 27).

1st Phase 3

2nd Phase 3

	Enrollment Target	Simufilam Treatment	Length of Treatment	Co-Primary Endpoints		Secondary Endpoints	
				Cognition Scale	Function Scale	Cognition + Function Scale	Dementia-related Behavior Scale
1 st Phase 3	~ 750 Subjects	100 mg	52-weeks	ADAS-Cog12	ADCS-ADL	iADRS	NPI ₁₂
2 nd Phase 3	~ 1,000 Subjects	100 mg or 50 mg	76-weeks	ADAS-Cog12	ADCS-ADL	iADRS	NPI ₁₂

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

Phase 3 Studies

Over 100 clinical investigational sites are now recruiting Alzheimer's patients.



- 52-week Phase 3 study, initiated Fall 2021.
- ≈ 750 subjects to be randomized (1:1) to simufilam 100 mg or placebo twice daily.
- Co-primary efficacy endpoints are ADAS-Cog12, a cognitive scale, and ADCS-ADL, a functional scale.
- A secondary efficacy endpoint is iADRS, a clinical tool that combines cognitive functional scores from ADAS-Cog & ADCS-ADL.
- Other secondary endpoints include plasma biomarkers of disease and NPI to assess dementia-related behavior.



- 76-week Phase 3 study, initiated Fall 2021.
- ≈ 1,000 subjects to be randomized (1:1:1) to simufilam 100 mg, 50 mg or placebo twice daily.
- Co-primary efficacy endpoints are ADAS-Cog12, a cognitive scale, and ADCS-ADL, a functional scale.
- A secondary efficacy endpoint is iADRS, a clinical tool that combines cognitive functional scores from ADAS-Cog & ADCS-ADL.
- Other secondary endpoints include CSF, plasma and imaging biomarkers of disease and NPI to assess dementia-related behavior.

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 is an early-stage product candidate, benefiting from long-term scientific & financial support from NIH.*
- *Lower priority program as compared to simufilam.*
- *SavaDx was evaluated for its ability to detect treatment effects of simufilam versus placebo in a Phase 2b, randomized, controlled study in patients with Alzheimer's. This SavaDx clinical dataset was presented July 2021 at AAIC. Erratum: the AAIC data and data analysis are correct, however, visual errors that were not caught in proofing were disclosed by the Company September 2021.*



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.
- We do not have issued patents in the U.S. for SavaDx. In the U.S., we believe SavaDx may be protected by trade secrets, know-how and other proprietary rights technology.

Financials

Eric Schoen - Chief Financial Officer

Financials

Nasdaq ticker: SAVA

Shares Outstanding

≈ 40.0 million

Financials at December 31, 2021

Cash Balance

≈ \$233.4 million

Debt

none

Est. Cash Use for Operations in the 1st Half of 2022 is Approximately \$25 to \$30 million.

Thank you!



CASSAVA
sciences

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/)

Erratum: Figure 12 contains an image showing 12 control bands; it should show 13. This visual error was not caught in proofing. The data analysis was based on all 13 control bands. This error does not impact data conclusions.

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>

Erratum: There is one duplicated panel in Figure 8; the publisher printed a correction. This error does not impact data conclusions.