CASSAVA sciences

We Focus on Alzheimer's disease

February 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; the FDA's response to a Citizen's Petition filed against simufilam; 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; results of our EOP2 meeting with FDA; our ability to expand therapeutic indications for simufilam outside of Alzheimer's disease; 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, 2020, as supplemented by the section entitled "Risk Factors" in our Quarterly Report on Form 10-Q for the quarter ended September 30, 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).

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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 are being 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.
- In 2H:2021, we initiated a Phase 3 clinical program with simufilam.
- SavaDx, our blood-based investigational diagnostic candidate, is in early-stage development.

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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 and Robertson Stephens & Company

Robert Gussin, PhD
Formerly, CSO & Corporate VP, Science and Technology, Johnson & Johnson

Patrick Scannon, MD/PhD
Formerly, Founder & CSO/CMO - XOMA Corporation

Richard Barry
Founding Partner, Portfolio Manager, Eastbourne Capital

Michael O'Donnell
Partner, Orrick LLP

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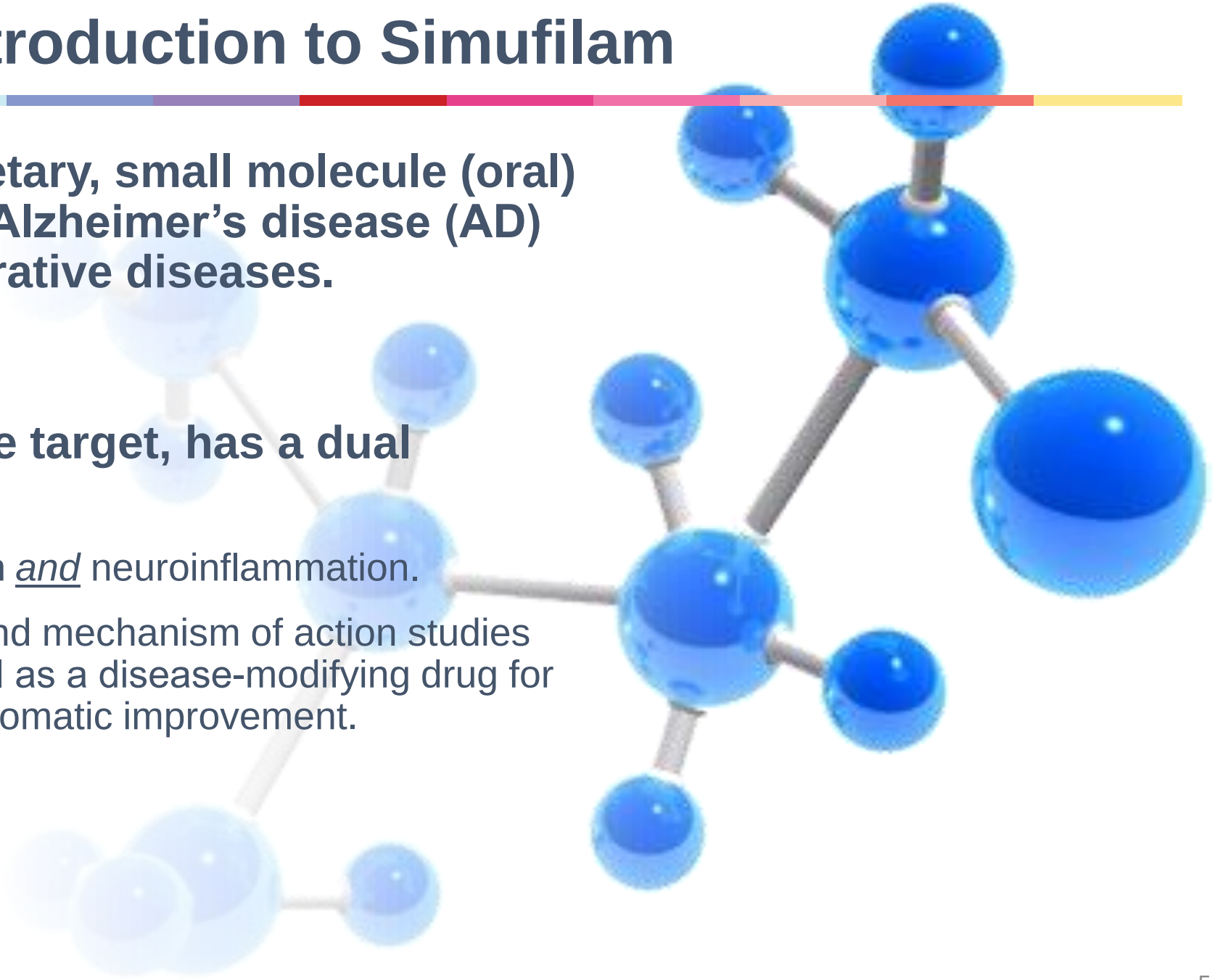
Introduction to Simufilam

- **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/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 future Phase 3 studies.*

On-going

- ❑ *Open-label study in Alzheimer's patients.*
  Status: fully-enrolled
- ❑ *Randomized, placebo-controlled Cognition Maintenance Study (CMS) in Alzheimer's patients.*
  Status: enrolling
- ❑ *Two Phase 3 studies under FDA special Protocol Assessments in Alzheimer's patients.*
  Status: enrolling

In 2nd Half 2021, we initiated a Phase 3 program with simufilam in Alzheimer's disease.

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Science & Technology

Lindsay Burns, PhD – SVP Neuroscience

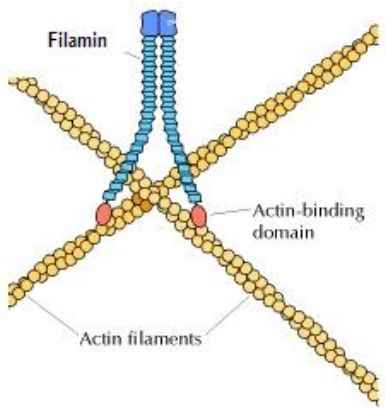
Nadav Friedmann, PhD/MD – Chief Medical Officer

Jim Kupiec, MD - Chief Clinical Development Officer

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 <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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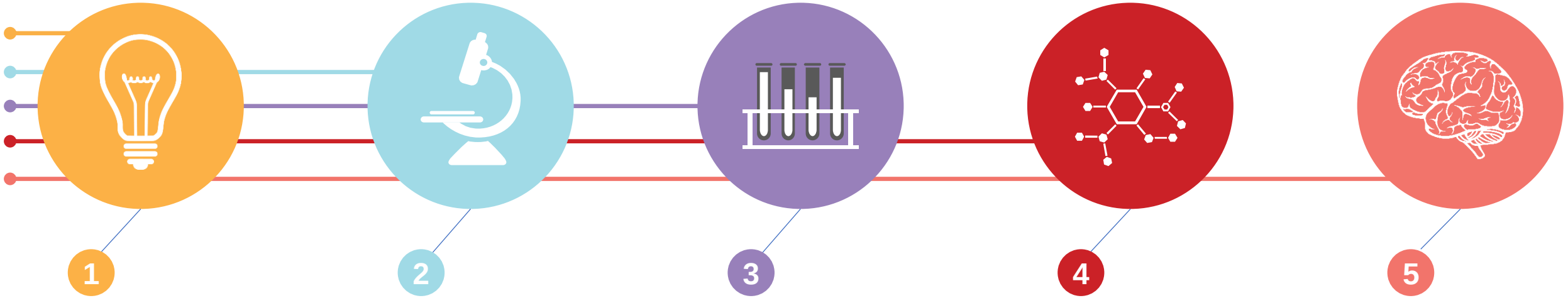
10+ Year In-house Discovery/Development Program



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

2009
Discovery that altered FLNA links to α7nAChR when Aβ signals.

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

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

2017 - present
IND filing. Clinical testing of simufilam.

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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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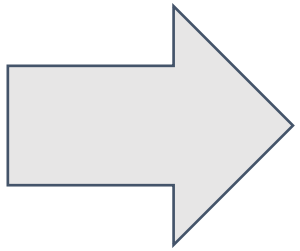
Clinical Hypothesis

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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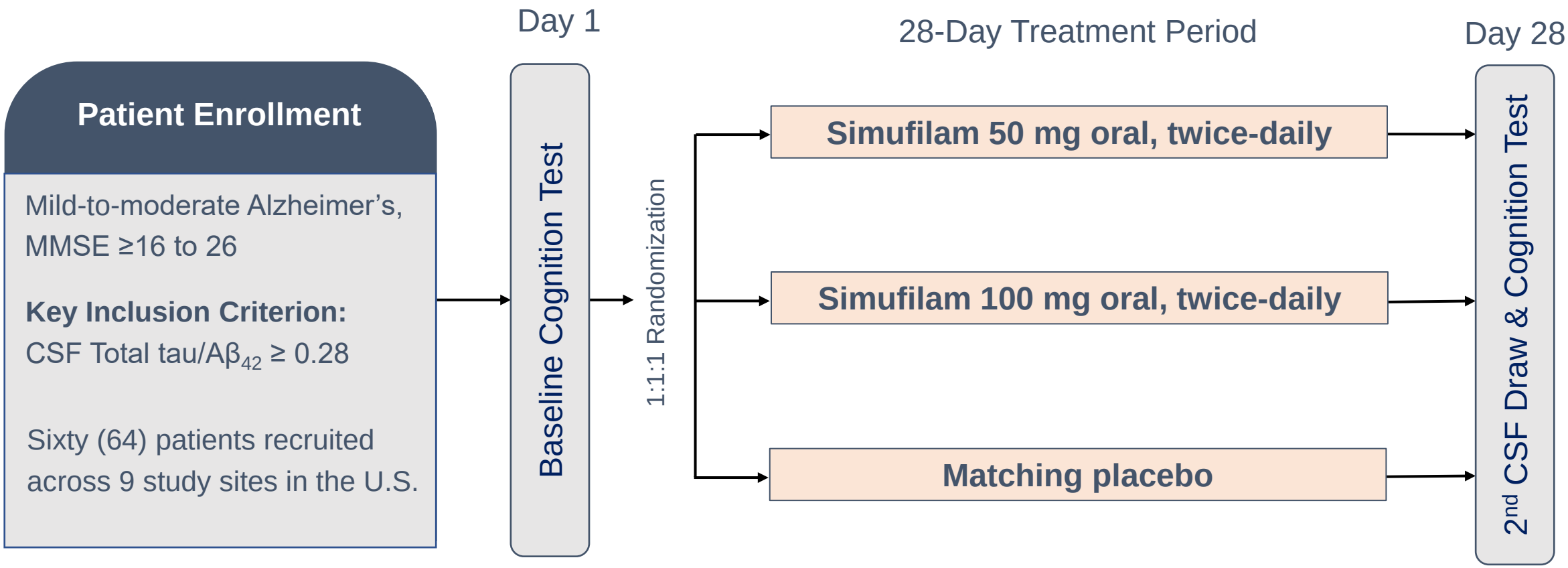
Phase 2b - Study Design

Double-blind, Randomized, Placebo-controlled, Multi-center, 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.**

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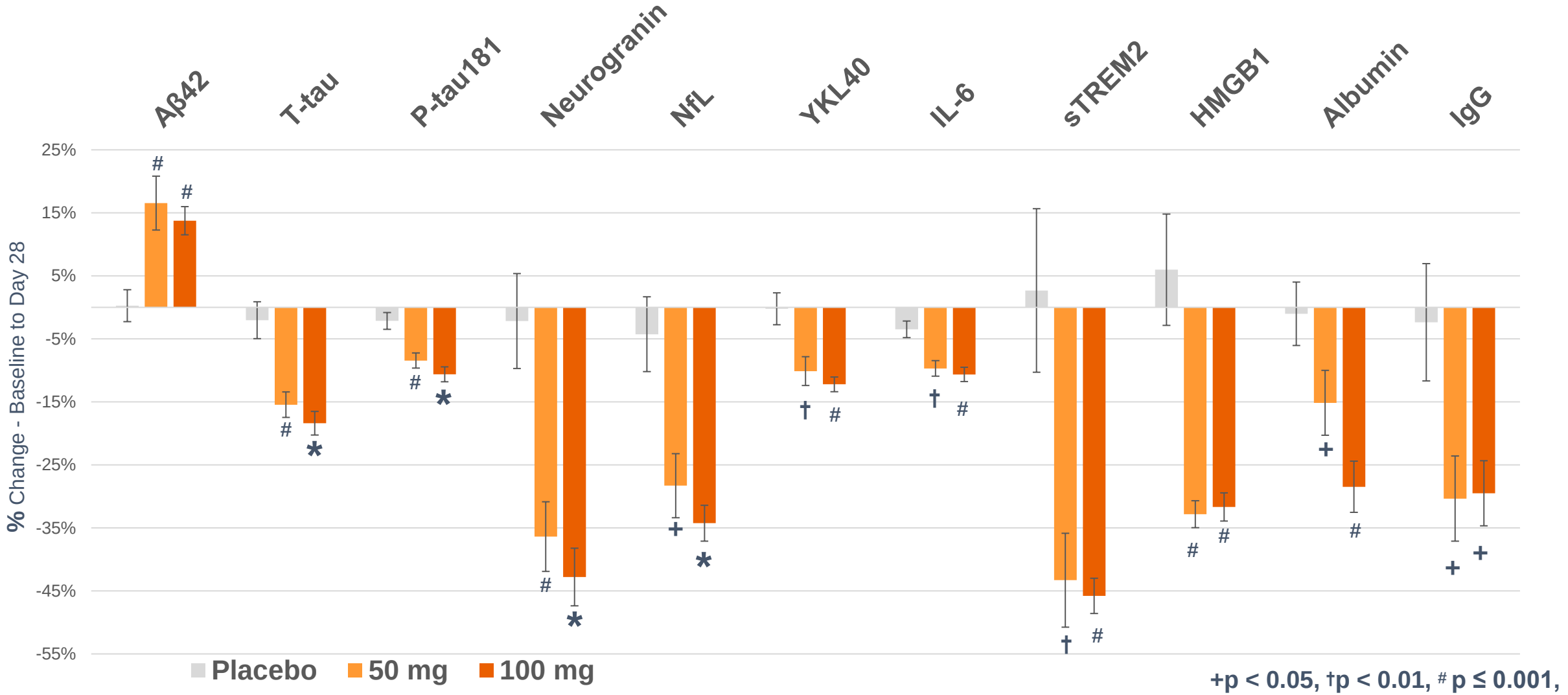
Phase 2b Summary of Results - CSF Biomarkers



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

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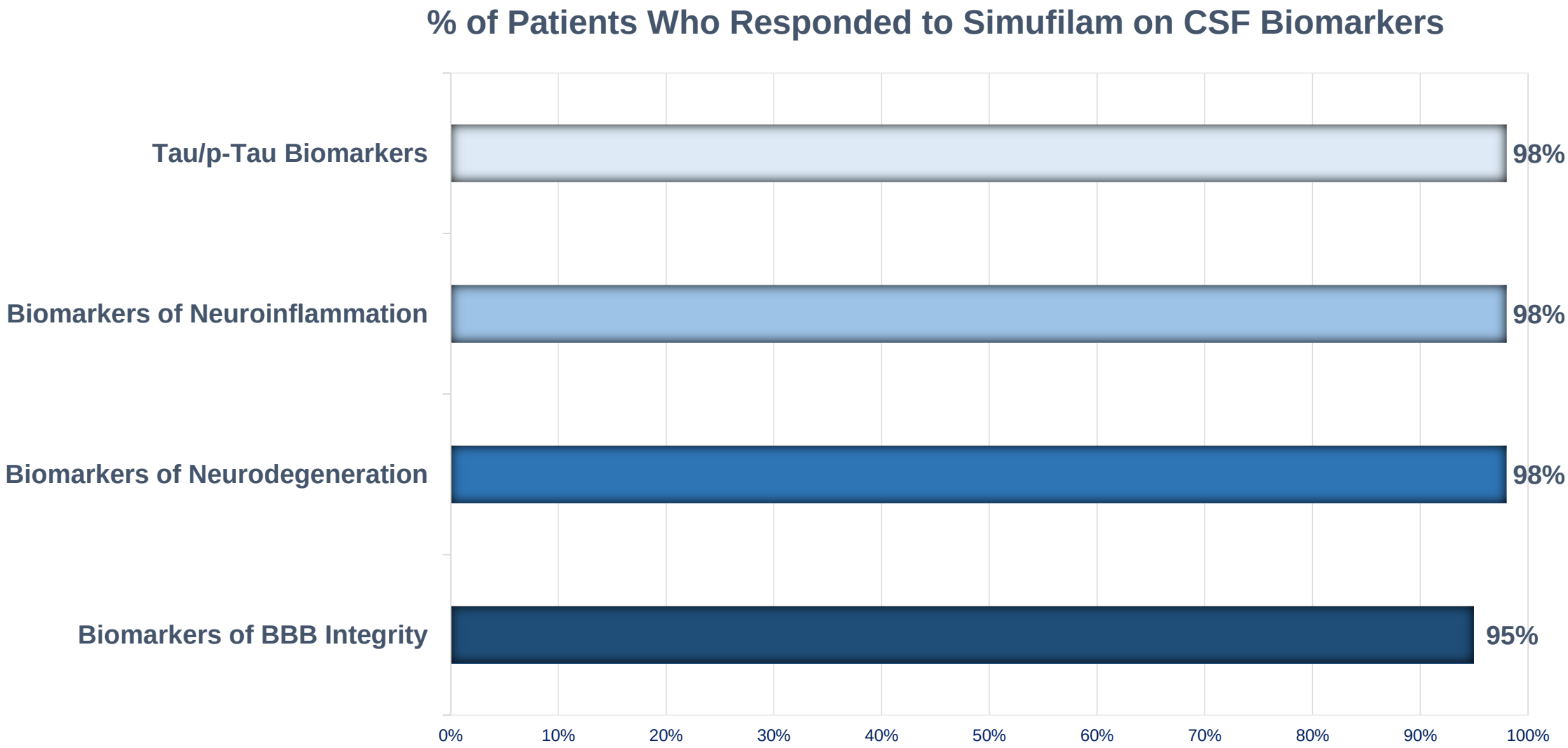
Phase 2b Results – Patient Responder Analysis



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Phase 2b 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, including a Phase 3 clinical program.**

In 2nd Half 2021, we initiated a Phase 3 program with simufilam in Alzheimer's disease.

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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: ~ 200+ study subjects from 16 investigator sites in the U.S. and Canada.

- **We conducted pre-planned interim analyses on 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.

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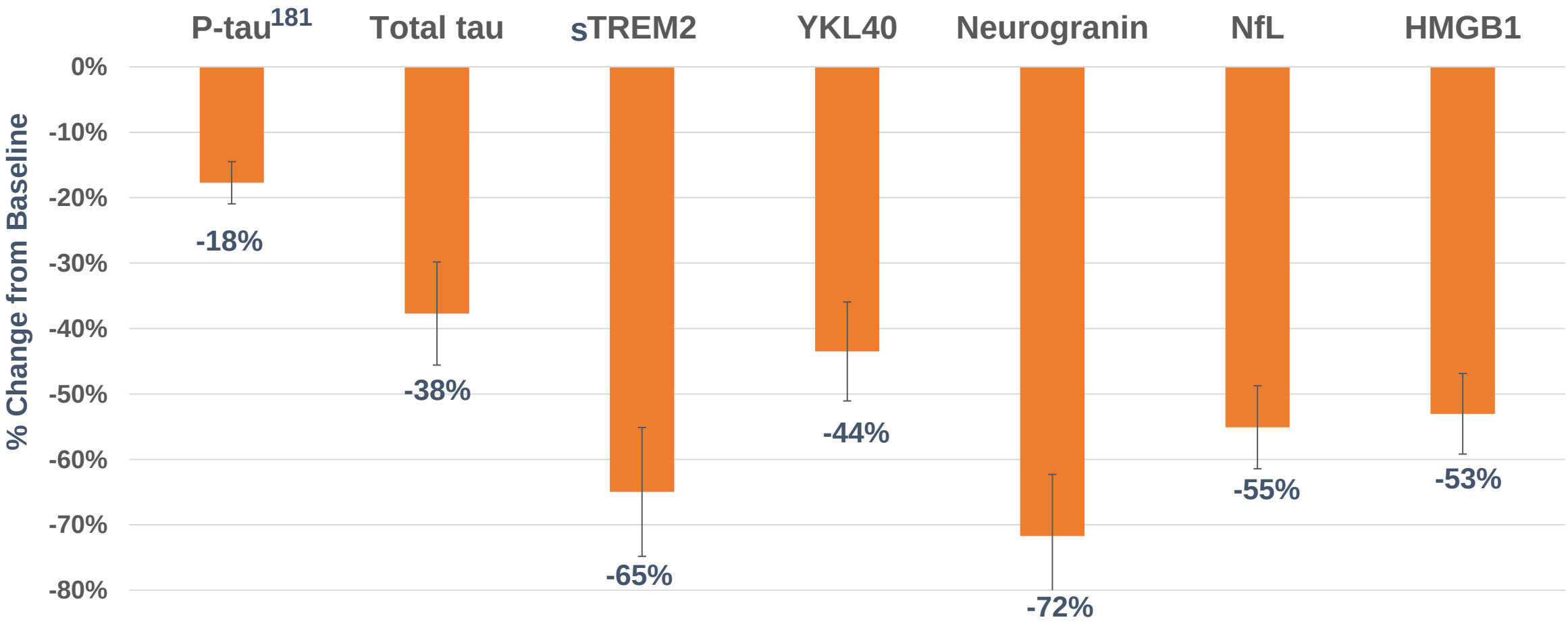
Open-label Study - Safety

- **Simufilam is safe and well-tolerated through the 12-month interim analysis.**
- **No drug-related serious adverse events.**
- **<10% dropout rate.**

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



P < 0.00001 for all by paired *t* test.

Not shown: CSF $A\beta_{42}$ increased significantly (+84%), as expected.

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.

P < 0.001 by paired *t* test: Baseline vs. 12 Months

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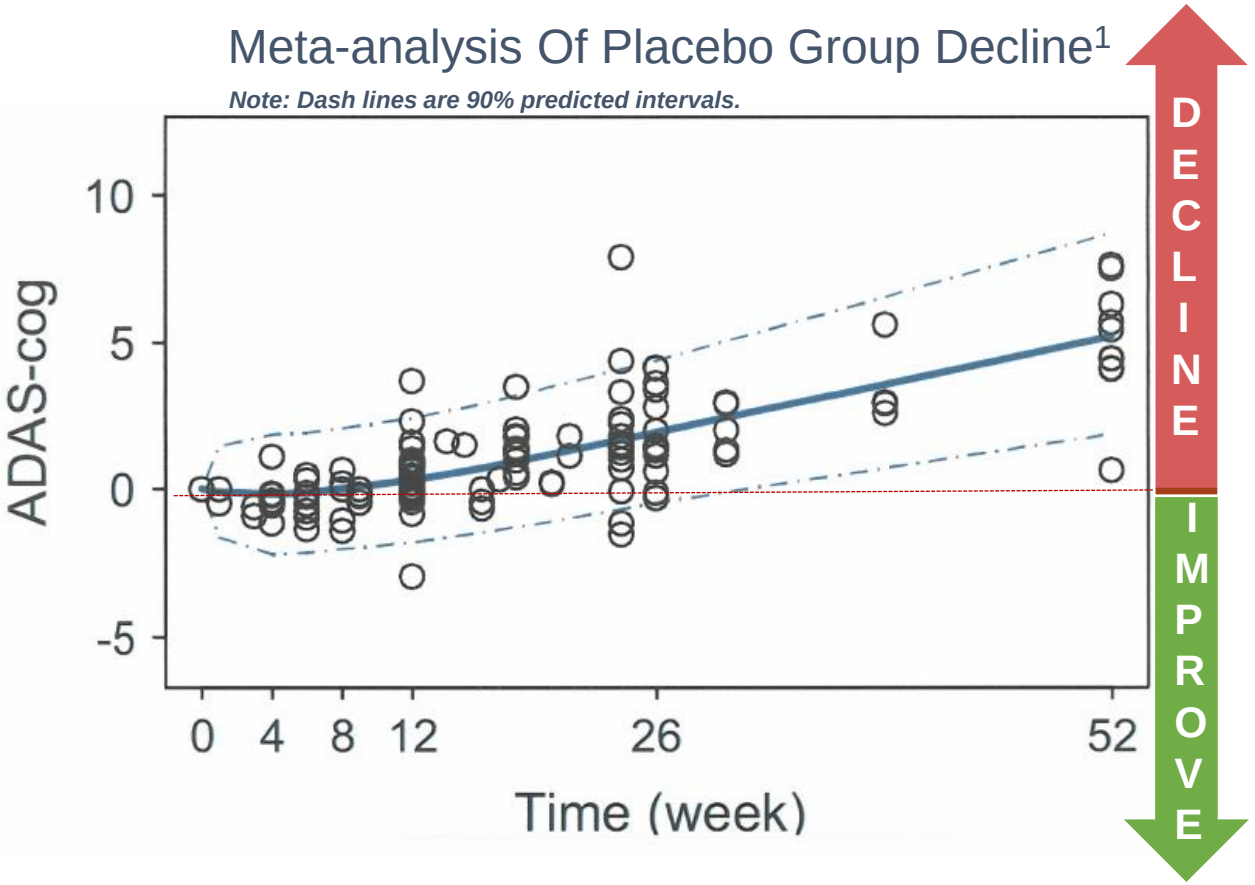
Expected Rate of Cognitive Decline in AD - Literature



- **Cognitive decline was reported in a published, meta-analysis of 20,000 patients with mild-to-moderate AD in randomized, controlled trials[1].**
  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 AD[2]:**
  5.2 point average decline over 18 months on ADAS-Cog among study subjects who were administered placebo in randomized, controlled trials.

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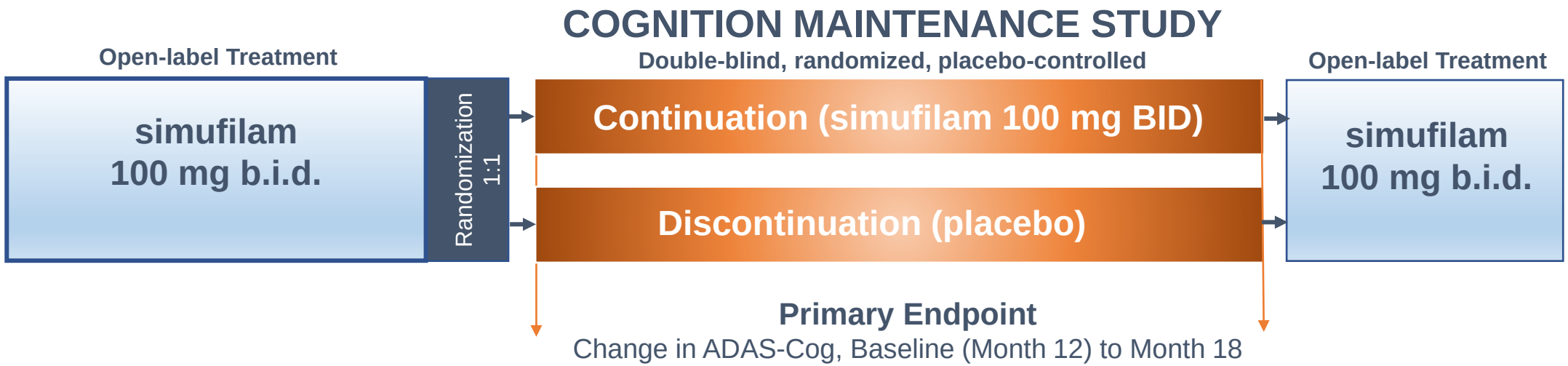
Sources:

[1] *Disease Progression Meta-analysis Model in Alzheimer's disease* (Ito, et al., Pfizer Global Research), Alzheimer's & Dementia 6 (2010) 39-53

[2] *EMERGE and ENGAGE Topline Results (2020), https://investors.biogen.com/static-files/f91e95d9-2fce-46ce-9115-0628cfe96e83*

Cognition Maintenance Study (CMS)

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



Study was initiated May 2021, as of September 2021 >35 subjects enrolled.

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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 an upcoming and 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.**

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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 (MMSE 16 to 27).

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

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

				Co-Primary Endpoints		Secondary Endpoints	
	Enrollment Target	Simufilam Treatment	Length of Treatment	Cognition Scale	Function Scale	Cognition + Function Scale	Dementia-related Behavior Scale
1st Phase 3	~ 750 Subjects	100 mg	12 Months	ADAS-Cog12	ADCS-ADL	iADRS	NPI_{12}
2nd Phase 3	~ 1,000 Subjects	100 mg or 50 mg	18 Months	ADAS-Cog12	ADCS-ADL	iADRS	NPI_{12}

Phase 3 Program Initiated 2nd Half 2021.

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

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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.*

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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 @ Sept 30, 2021:	**≈ $241.5 million**
Debt:	***none***
Est. Cash Use for Operations, FY 2021:	**≈ $25 to $30 million**

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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.**

- **In the U.S., there is no patent protection for SavaDx, which we believe can be protected by trade secrets, know-how and other proprietary rights technology.**

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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/
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.

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