



# Forward-Looking Statements & Other Notices

*Cassava Sciences is in the business of new drug discovery and development. Our research and development activities are long, complex, costly and involve a high degree of risk. Holders of our common stock should carefully read our Annual Report on Form 10-K in its entirety, including the risk factors therein. Because risk is fundamental to the process of drug discovery and development, you are cautioned to not invest in our publicly traded securities unless you are prepared to sustain a total loss of the money you have invested. Only a small number of research and development programs result in regulatory approval and subsequent commercialization of a product. In addition, our clinical results from earlier-stage clinical trials may not be indicative of full results or results from later-stage or large-scale clinical trials and do not ensure or imply regulatory approval. You should not place undue reliance on our earlier-stage clinical trial results we present or publish.*

*Simufilam is our investigational drug product candidate. It is not approved by any regulatory authority in any jurisdiction and its safety, efficacy or other desirable attributes, if any, have not been established in patients. Data from our clinical studies to date are all inherently exploratory in nature, should be interpreted with caution and should not be interpreted as clinical evidence of therapeutic safety or benefit for simufilam.*

*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 ability to extend our existing open-label extension trials, as contemplated or at all; the design, scope, conduct or intended purpose of our two-year, open-label safety study or our Phase 3 program of simufilam in patients with Alzheimer's disease; the ability of simufilam to provide patients with beneficial drug effects; the apparent ability of simufilam to favor patients with mild Alzheimer's disease; the apparent safety or tolerance of simufilam in our open-label clinical trials; our current expectations regarding timing of clinical data for our Phase 3 studies; any expected clinical results of Phase 3 studies; the treatment of people with Alzheimer's disease dementia; the interim safety or efficacy of simufilam, if any, in people with Alzheimer's disease dementia; any findings or recommendations by the DSMB relating to the interim safety of simufilam in our on-going Phase 3 clinical trials; interim MRI safety data for the Phase 3 program, including ARIA; the risk of current or future findings of treatment-emergent ARIA in our clinical program of simufilam; the suitability of clinical data from our Phase 3 program to support the filing of an NDA; our ability to obtain FDA approval for simufilam, even with a potential NDA filing and positive clinical Phase 3 results and data; expected cash use in future periods; comments made by our employees regarding simufilam, drug effect, and the treatment of Alzheimer's disease; and potential benefits, if any, of our product candidates. These statements may be identified by words such as "may," "anticipate," "believe," "could," "expect," "would", "forecast," "intend," "plan," "possible," "potential," and other words and terms of similar meaning.*

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# Introduction to Cassava Sciences



We are a biotechnology company based in Austin, Tx.

We are developing an innovative, oral drug candidate for people with Alzheimer's disease.

Our science is based on stabilizing—but not removing—a critical protein in the brain.

*Our lead drug candidate, simufilam, is in Phase 3 clinical testing in patients with Alzheimer's disease.*

*Top-line results of our 52-week Phase 3 (Re-THINK) are expected by year-end 2024.*

# Cassava Sciences – Independent Directors



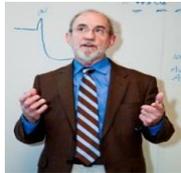
**Sanford Robertson**

In Memoriam



**Robert Gussin, PhD**

Formerly, Chief Scientific Officer  
Johnson & Johnson



**Patrick Scannon, MD/PhD**

Formerly, Founder & Chief Scientific Officer  
XOMA Corporation



**Michael O'Donnell**

Partner, Orrick LLP



**Claude Nicaise, MD**

Formerly, SVP Global Regulatory Affairs  
Alexion Pharmaceuticals.  
VP of Regulatory Science, Bristol-Myers Squibb



**Pierre Gravier, MS**

Chief Financial Officer, PTC Therapeutics.  
Formerly Managing Director, Healthcare Group,  
Perella Weinberg



**Robert Anderson**

CEO, Cyber Defense Labs;  
Formerly, FBI Executive Assistant Director of the Criminal,  
Cyber, Response, and Services Branch

# Cassava Sciences - Senior Management

*Years of experience with scientific and drug innovations.*



**Richard Barry -  
President & Chief Executive  
Officer**

Founding Partner, Portfolio Manager,  
Eastbourne Capital



**Michael Zamloot – SVP, Technical Operations**



**Ciba-Geigy**



**Jim Kupiec, MD – Chief Medical Officer**



**Ciba-Geigy**



**Michael Marsman, PharmD – SVP, Regulatory  
Affairs**



**Eric Schoen - Chief Financial Officer**



**PRICEWATERHOUSECOOPERS**



**Chris Cook – SVP, General Counsel**



# Alzheimer's Disease: a Significant Unmet Need

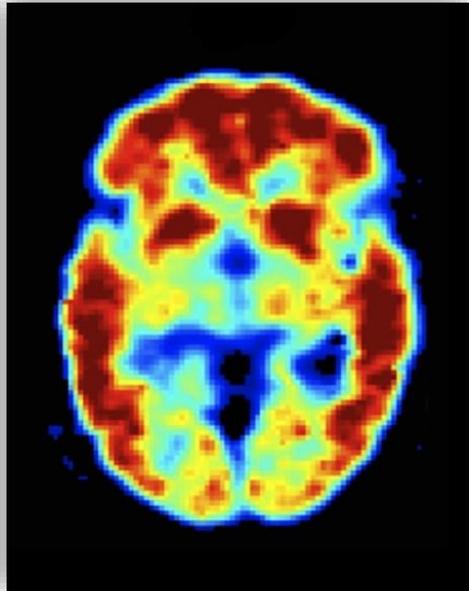
A handwritten signature in black ink, appearing to read 'Alzheimer', with a small dot above the 'i'.

Signature of Alois Alzheimer, circa 1915

**Alzheimer's disease outranks cancer, stroke and heart attack as most-feared chronic disease by retirees, according to a study.<sup>1</sup>**

**Cassava Sciences sees an opportunity to serve patients, create value for stakeholders.**

# Ultimately, a Fatal Disease



Alzheimer's disease (AD) is a chronic, progressive neurological disorder.

AD causes memory loss, difficulty speaking & understanding, behavior changes, other issues.

*Eventually, the AD patient is unable to perform daily functions.*

# Rx Drugs for Alzheimer's Disease



## Older drugs can address clinical symptoms for some time.

- donepezil (e.g., Aricept®) – oral cholinesterase inhibitor, FDA approval 1996, all stages of disease
- galantamine (e.g., Razadyne®) – oral cholinesterase inhibitor, FDA approval 2001, mild-to-moderate disease
- rivastigmine (e.g., Exelon®) – cholinesterase inhibitor, oral or patch, FDA approval 1997, mild-to-moderate disease
- memantine (e.g., Namenda®) – oral NMDA antagonist, FDA approval 2003, moderate-to-severe disease



## More recently, antibody drugs slow disease progression by targeting amyloid in the brain.

- aducanumab (Aduhelm® – Biogen) - IV infusion, FDA approval June 2021 in MCI/mild AD, withdrawn from market 2024
- lecanemab (Leqembi® – Eisai/Biogen) – 2x month IV infusion, FDA approval Jan 2023 in MCI/mild AD
- donanemab (Eli Lilly) – monthly IV infusion, MCI/mild AD, FDA approval July 2024

# Anti-amyloid Antibodies for Alzheimer's Disease

- **Aggregate efficacy data from Phase 3 trials of anti-amyloid antibodies suggest benefits in early AD.**
  - Twice-monthly IV infusions of lecanemab (Leqembi®/Eisai-Biogen) slowed cognitive decline on average by ~25% over 18 months compared to placebo in the Clarity-AD trial.<sup>1</sup> Efficacy results varied by gender and APOE genotype.
  - Monthly IV infusions of donanemab (Lilly) slowed decline on iADRS, a cognitive/functional composite, on average by ~35% over 18 months compared to placebo in low-medium tau AD patients and by ~22% in all patients in the Trailblazer-Alz trial.<sup>2</sup>
- **Safety data from Phase 3 trials suggest a complex risk-benefit profile for patients.**
  - The entire class of drugs is associated with amyloid-related imaging abnormalities (ARIA), such as brain bleeding or swelling.
  - Frequent MRI scans are needed to monitor for ARIA, a risk especially elevated in APOE4 allele carriers.
  - Other possible side effects (brain shrinkage, infusion reactions, interactions with anti-coagulants, etc.) may add risks.
- **Complex treatment logistics suggest a health burden, inequity and access disparities.**
  - Timely IV infusions, frequent MRIs and APOE genotyping require access to infusion centers, imaging centers and integrated care.
  - Treatment logistics may limit access in rural areas; co-pays, non-reimbursed expenses, etc. may drive affordability issues.
  - Precise diagnosis of early AD dementia, judicious selection of appropriate patients, etc. may be challenging outside of specialist clinics.

*Alzheimer's is a complex, chronic disorder.*

*We believe reducing the burden of AD will require novel drugs and combination therapy.*

# Simufilam – A New Type of Drug For Alzheimer’s

Simufilam is a small molecule (oral) drug candidate.

Simufilam targets altered filamin A protein, which is found in the Alzheimer’s brain.

Simufilam is an in-house discovery/development program.

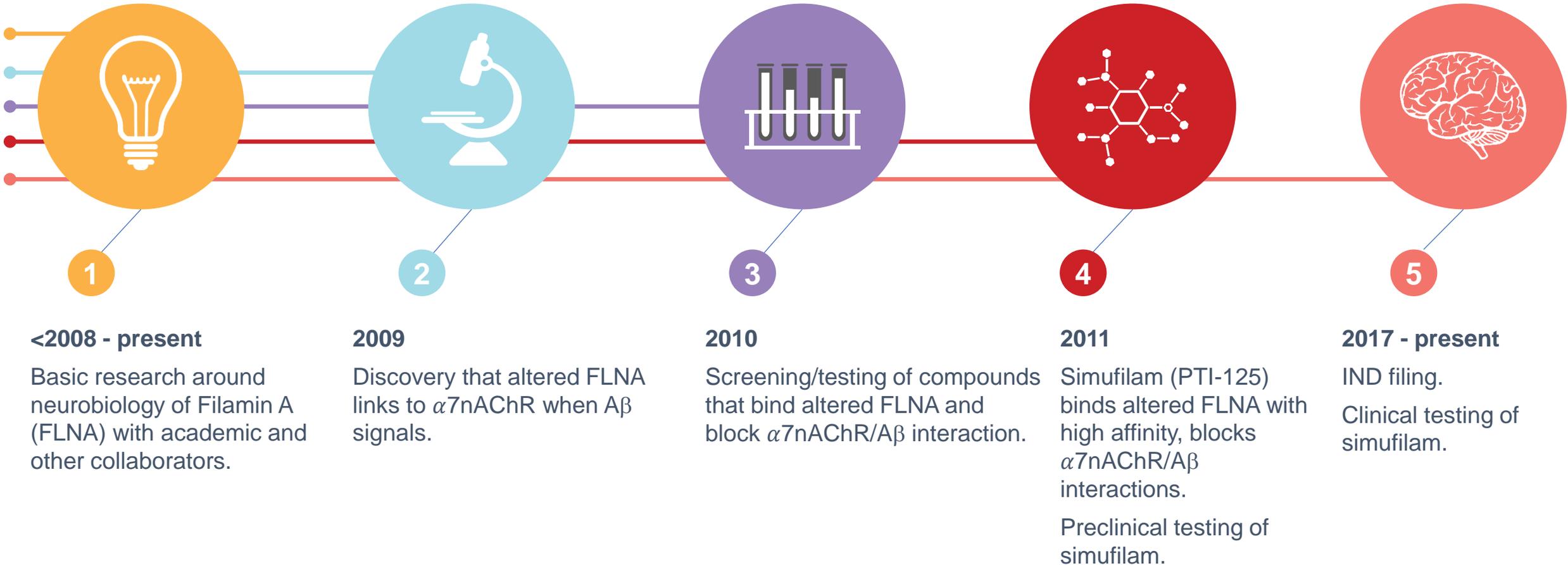
***We own exclusive, worldwide rights to simufilam.***

Not actual photo of simufilam tablet.

# Science and Basic Research

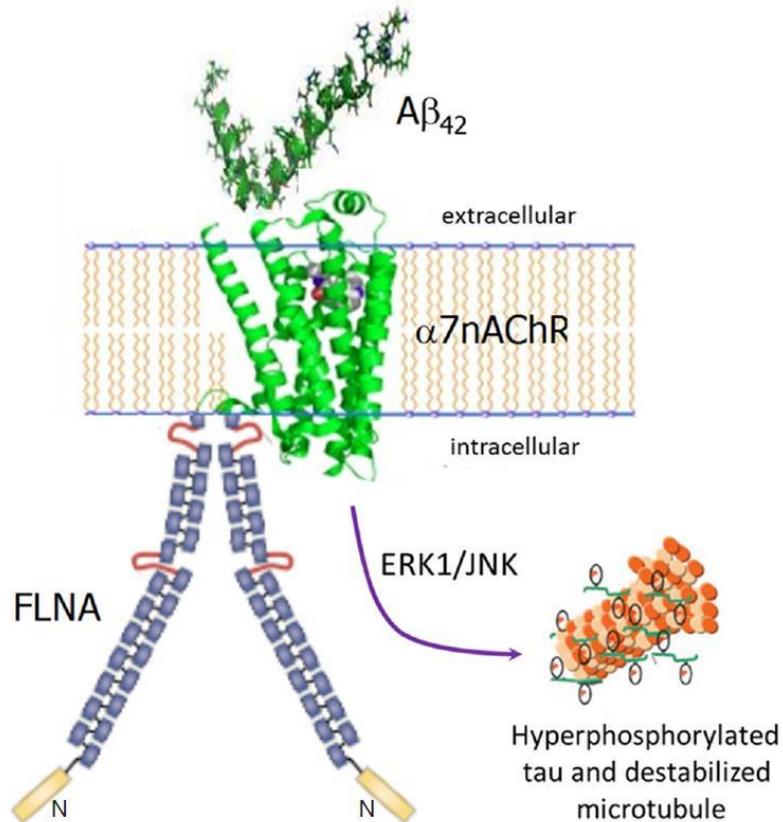


# In-house Discovery/Development Program



# Mechanism of Action, Simplified

*Simufilam targets an altered form of filamin A protein found in the Alzheimer's brain.*



- i. Scaffolding proteins, such as filamin A (FLNA), link other proteins into stable, healthy conformations.
- ii. The AD brain has an altered form of FLNA – Aβ<sub>42</sub> binds α7nAChR and recruits FLNA, altering its shape.
- iii. Altered FLNA *enables* Aβ neurotoxicity – altered FLNA linkage to α7nAChR enables high-affinity binding of Aβ<sub>42</sub> for α7nAChR and cell signaling that hyperphosphorylates tau.
- iv. Simufilam *disables* Aβ neurotoxicity by binding to altered FLNA, restoring its proper shape/function – disrupts its linkage to α7nAChR, stops Aβ<sub>42</sub> signaling and tau hyperphosphorylation.

# Filamin A Research - an Emerging Area of Neuroscience



Molecular Neurobiology (2023) 60:1021–1039  
<https://doi.org/10.1007/s12035-022-03121-w>

## Direct and Indirect Effects of Filamin A on Tau Pathology in Neuronal Cells

Stéphanie Levert<sup>1,2</sup> · Julie Pilliod<sup>1,2</sup> · Étienne Aumont<sup>3,4</sup> · Sandrine Armanville<sup>1,2</sup> · Cyntia Tremblay<sup>5,6</sup> · Frédéric Calon<sup>5,6</sup> · Nicole Leclerc<sup>1,2</sup>

Received: 24 August 2022 / Accepted: 4 November 2022 / Published online: 18 November 2022  
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## Science Translational Medicine

### EPILEPSY

## Filamin A inhibition reduces seizure activity in a mouse model of focal cortical malformations

Longbo Zhang<sup>1,2</sup>, Tianxiang Huang<sup>1,2</sup>, Shannon Teaw<sup>1</sup>, Lena H. Nguyen<sup>1</sup>, Lawrence S. Hsieh<sup>1</sup>, Xuan Gong<sup>1,2</sup>, Lindsay H. Burns<sup>3</sup>, Angélique Bordey<sup>1\*</sup>

Epilepsy treatments for patients with mechanistic target of rapamycin (mTOR) disorders, such as tuberous sclerosis complex (TSC) or focal cortical dysplasia type II (FCDII), are urgently needed. In these patients, t

## Science Advances

SCIENCE ADVANCES | RESEARCH ARTICLE

### DISEASES AND DISORDERS

## Actin-binding protein filamin-A drives tau aggregation and contributes to progressive supranuclear palsy pathology

Koyo Tsujikawa<sup>1,2,3</sup>, Kohei Hamanaka<sup>4</sup>, Yuichi Riku<sup>1,3</sup>, Yuki Hattori<sup>6</sup>, Norikazu Hara<sup>7</sup>, Yohei Iguchi<sup>1</sup>, Shinsuke Ishigaki<sup>1,8</sup>, Atsushi Hashizume<sup>1,9</sup>, Satoko Miyatake<sup>4,10</sup>, Satomi Mitsuhashi<sup>4,11</sup>, Yu Miyazaki<sup>1</sup>, Mayumi Kataoka<sup>1</sup>, Li Jiayi<sup>1</sup>, Kelzo Yasui<sup>2</sup>, Satoshi Kuru<sup>3</sup>, Haruki Kolke<sup>1</sup>, Kenta Kobayashi<sup>12</sup>, Naruhiko Sahara<sup>13</sup>, Norio Ozaki<sup>14</sup>, Mari Yoshida<sup>3</sup>, Akiyoshi Kakita<sup>13</sup>, Yuko Saito<sup>10</sup>, Yasushi Iwasaki<sup>3</sup>, Akinori Miyashita<sup>7</sup>, Takeshi Iwatsubo<sup>17</sup>, Japanese Alzheimer's Disease Neuroimaging Initiative (J-ADNI)†, Takeshi Ikeuchi<sup>7</sup>, Japanese Longitudinal Biomarker Study in PSP and CBD (JALPAC) Consortium‡, Takaki Miyata<sup>6</sup>, Gen Sobue<sup>8</sup>, Naomichi Matsumoto<sup>4</sup>, Kentaro Sahashi<sup>1</sup>, Masahisa Katsuno<sup>1,9\*</sup>

While amyloid- $\beta$  lies upstream of tau pathology in Alzheimer's disease, key drivers for other tauopathies, including progressive supranuclear palsy (PSP), are largely unknown. Various tau mutations are known to facilitate tau aggregation, but how the nonmutated tau, which most cases with PSP share, increases its propensity to aggre-

# Independent Validation of Simufilam Activity / FLNA Target

- **2020 Yale publication: simufilam is effective in mouse model of pediatric epilepsy.**
  - Simufilam reduced neuronal malformations and seizures.
  - The model was dependent on FLNA overexpression; improvements also seen with RNA knockdown of FLNA.
- **2023 conference: Milan scientists showed simufilam effects on pituitary tumors.**
  - Simufilam reduced phosphorylation of FLNA in patient pituitary tumor cells and a rat tumor cell line.
  - Simufilam improved functioning of somatostatin receptor type 2 (SST2).
  - Simufilam enhanced efficacy of octreotide (Sandostatin<sup>®</sup>), SST2 agonist that is standard of care for pituitary tumors.
- **2023 Institut Cochin publication: simufilam reduces  $A\beta_{42}$  binding to  $\alpha 7nAChR$** 
  - Cell-based assay uses TR-FRET to test drug candidates' ability to disrupt  $A\beta_{42}$  binding to  $\alpha 7nAChR$ .
  - Simufilam potently reduced  $A\beta_{42}$  binding at a 12 picomolar  $IC_{50}$ .
- **2022 & 2023 U. Quebec publications: higher levels of insoluble FLNA in AD brain.**

# SavaDx: an Investigational Diagnostic for Alzheimer's

- The underlying science for simufilam supports the development of a diagnostic technology to detect Alzheimer's in blood.
- SavaDx is an early-stage product candidate and is still a 'research-use only' exploratory biomarker.
- Working with third parties, we are evaluating the use of mass spectrometry to detect FLNA.
- SavaDx is a lower priority program compared to simufilam.



# Clinical Proof-of-Concept



# Open-label Study Results

## 12-month Open-label Study

January 24, 2023 Press Release<sup>1</sup>

Long-term Safety &  
Cognition Study in  
Alzheimer's Patients (N=220)



### Cassava Sciences Announces Positive Top-Line Clinical Results in Phase 2 Study Evaluating Simufilam in Alzheimer's Disease

- ADAS-Cog mean scores changed minimally over 1 year in patients with mild-to-moderate Alzheimer's disease treated with open-label simufilam tablets.
- 47% of patients improved on ADAS-Cog over 1 year, and this group improved by 4.7 points. An additional 23% of patients declined less than 5 points on ADAS-Cog over 1 year, and this group declined by 2.5 points.
- Mild patients responded better than patients with moderate Alzheimer's disease.
- Simufilam was safe, well tolerated.

**AUSTIN, Texas – January 24, 2023** – Cassava Sciences, Inc. (Nasdaq: SAVA), a biotechnology company, today announced positive top-line Phase 2 results for simufilam, its oral drug candidate for Alzheimer's disease dementia. This was an open-label safety study with exploratory efficacy endpoints. The study enrolled over 200 patients with mild-to-moderate Alzheimer's disease (MMSE 16-26). Study participants were administered open-label simufilam tablets 100mg twice daily for 1 year or more. Endpoints were measured at baseline (study entry) and month 12.

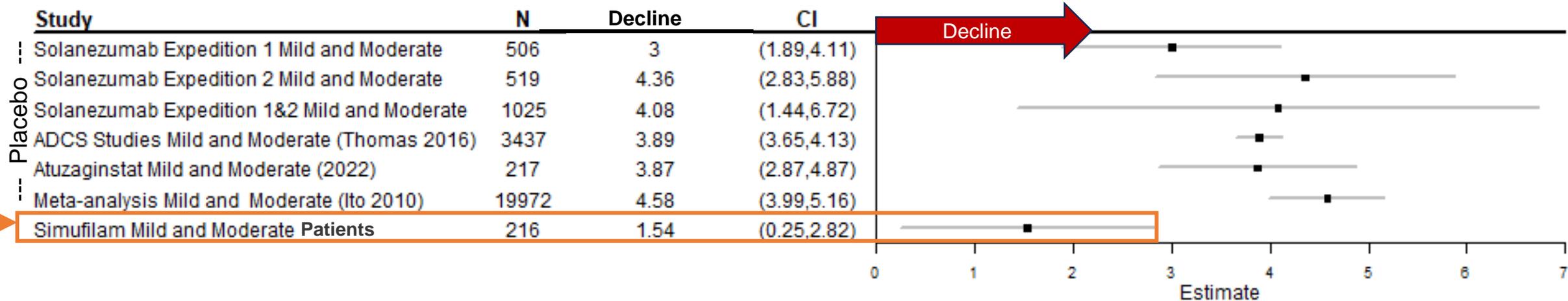
**Top-line Results – mean scores, baseline to month 12** (*lower is better, except for MMSE*):

- ADAS-Cog11 scores changed from 19.1 ( $\pm 9.2$ ) to 19.6 ( $\pm 13.3$ )
- MMSE scores changed from 21.5 ( $\pm 3.6$ ) to 20.2 ( $\pm 6.4$ )

# Open-label Study Results – mild-to-moderate AD patients

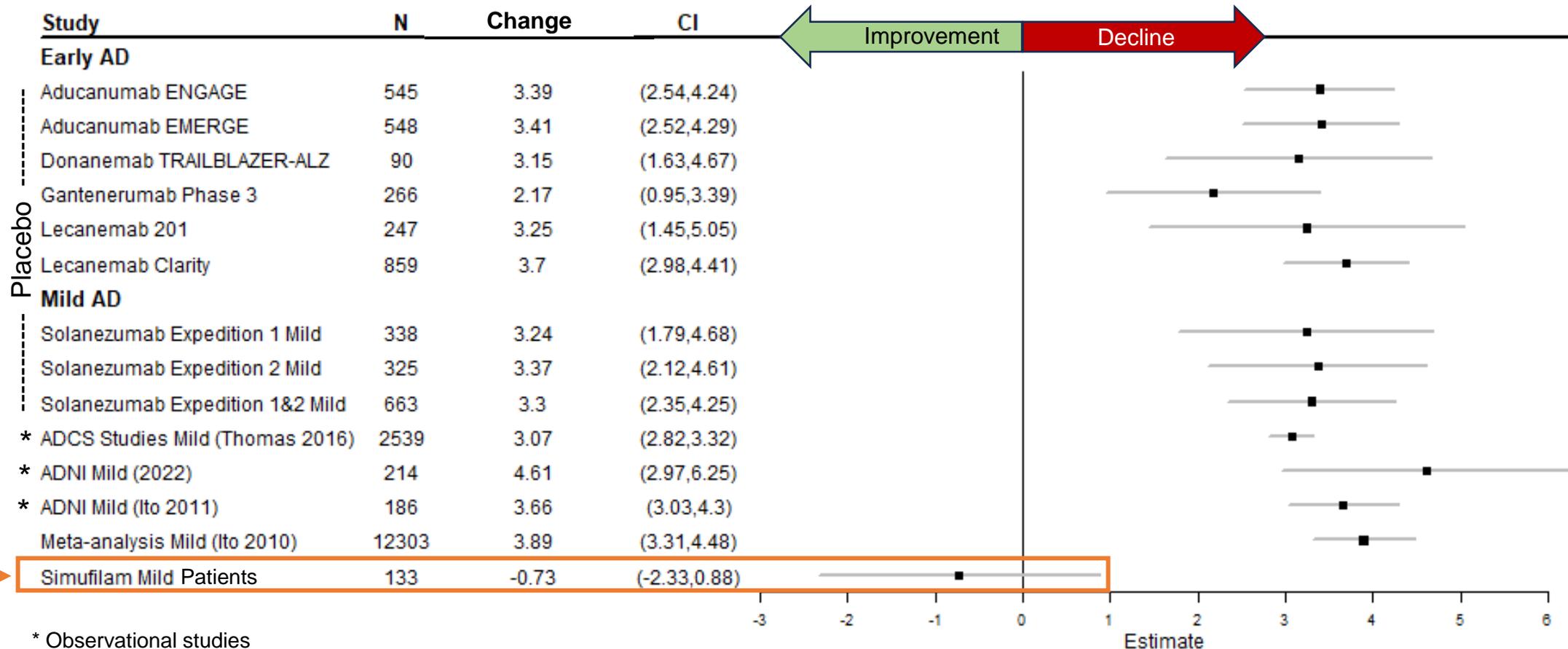
## Simufilam vs. Historical Placebo Controls in Patients with Mild-to-moderate AD<sup>1</sup>

Change in ADAS-Cog, baseline to 12 months



# Open-label Study Results – mild AD patients

Simufilam vs. Historical Placebo in Patients with Early or Mild AD<sup>1</sup>  
Change in ADAS-Cog, baseline to 12 months



\* Observational studies

# Randomized Withdrawal Study Results

## 6-month Randomized Withdrawal Study

(aka, Cognition  
Maintenance Study – CMS)

Randomized, Double-blind,  
Placebo-controlled Study in  
Alzheimer's Patients (N=157)

July 5, 2023 Press Release<sup>1</sup>



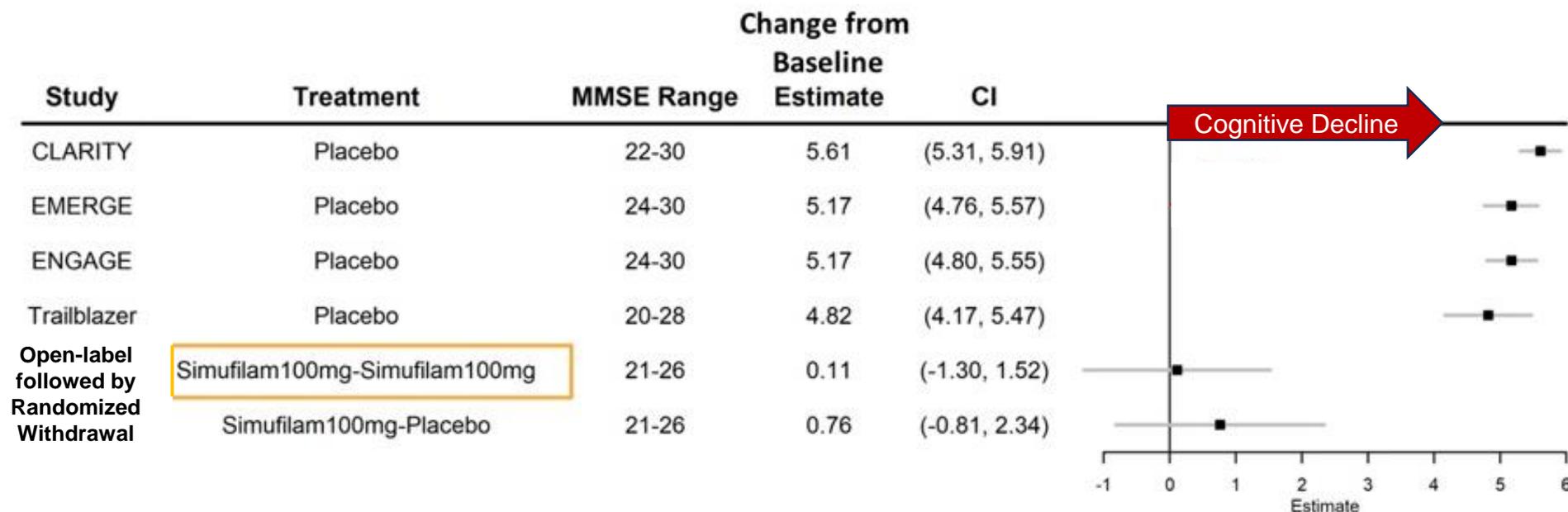
## Oral Simufilam Slowed Cognitive Decline in a Randomized Withdrawal Trial of Mild-to-Moderate Alzheimer's Disease

- Simufilam Slowed Cognitive Decline by 38% Versus Placebo Over 6 months in Patients with Mild-to-Moderate Alzheimer's Disease.
- Drug Effects Favored Mild Alzheimer's Disease.
- In Mild Alzheimer's, Simufilam Improved Cognition Scores Over 6 Months.
- In Mild Alzheimer's, Simufilam Stabilized Cognition Scores Over 18 Months.
- Oral Simufilam Continues to be Safe, Well Tolerated.

**AUSTIN, Texas – July 5, 2023** – Cassava Sciences, Inc. (Nasdaq: SAVA), a biotechnology company, today announced top-line clinical results from its Cognition Maintenance Study (CMS). The CMS is a small proof-of-concept study designed to demonstrate the effects of drug versus placebo in a randomized withdrawal trial design. The study enrolled 157 patients with mild-to-moderate Alzheimer's disease, a more advanced and difficult-to-treat stage of disease.

# Randomized Withdrawal (CMS) Study Results – mild patients

Mild AD patients (MMSE 21–26) on simufilam for 18 months showed no material decline in ADAS-Cog scores as a group, indicating stable cognition.<sup>1</sup>



Forest plot of historical declines on ADAS-Cog over 18 months in mild Alzheimer's (MMSE 20-30), placebo arms vs simufilam treatment.<sup>2</sup>

<sup>1</sup>'Simufilam100mg-Simufilam100mg' refers to mild AD patients (N=76) who received simufilam in both the 12-month open-label phase and the 6-month randomized withdrawal study/CMS; 'Simufilam100mg-Placebo' refers to patients who received simufilam in the open-label phase and placebo in the randomized withdrawal study/CMS.

<sup>2</sup> Forest plot by Pentara Corporation. Data was sourced from the placebo groups in randomized, controlled trials of monoclonal antibodies conducted by other sponsors in mild Alzheimer's disease (MMSE 20-30). Results shown for CLARITY P3 trial of Eisai's lecanemab; EMERGE and ENGAGE P3 studies of Biogen's aducanumab; and TRAILBLAZER P3 trial of Lilly's donanemab.

# No Decline in Cognition Scores in Mild AD Over 24 Months

- *Patients with mild Alzheimer's disease who received simufilam treatment continuously for two years (n=47) had no decline in ADAS-Cog scores ( $\pm 1.51$  SE) as a group.*
- *Patients with mild Alzheimer's who received simufilam treatment non-continuously (n=40) declined 1 point on ADAS-Cog ( $\pm 1.65$  SE) as a group. Non-continuous treatment consisted of one year on open-label drug, six months on placebo and six months back on open-label drug.*

From Feb 7, 2024, Press Release<sup>1</sup>



## No Decline in Cognition Scores in Patients with Mild Alzheimer's Disease Who Received Simufilam Continuously For 24 Months

- ADAS-Cog Scores Were Stable in a Group of Patients with Mild Alzheimer's Who Received Drug Candidate Simufilam Continuously, Baseline to Month 24.
- Mild Alzheimer's Patients Who Received Simufilam Non-Continuously Declined a Group Average of 1 Point on ADAS-Cog, Baseline to Month 24.
- Oral Simufilam Safe, Well-Tolerated.

**AUSTIN, Texas – February 7, 2024** – Cassava Sciences, Inc. (Nasdaq: SAVA), a biotechnology company, today reported top-line results of a two-year clinical safety study of simufilam, an investigational oral drug for the proposed treatment of Alzheimer's disease dementia. The study enrolled over 200 patients with mild to moderate Alzheimer's and consisted of two open-label treatment phases and a randomized, placebo-controlled withdrawal phase. Average changes in ADAS-Cog scores, baseline to month 24, indicate the following:

# Phase 3 Program



# Phase 3 Development Goals

- **Evaluate overall risk/benefit for simufilam b.i.d. versus placebo in a large AD population over 12 and 18 months.**
  - Long-term safety + potentially disease-modifying treatment effects.
  - Target study population is patients with mild-to-moderate AD (baseline MMSE 16-27) and who are also biomarker-positive for AD pathology, and who meet other inclusion/exclusion eligibility criteria of the study protocols.
- **Overarching goal is to generate sufficient clinical data to submit to FDA a 505(b)(1) New Drug Application (NDA) that shows “*an adequate basis for drug approval.*”**

# Two (almost) Identical Phase 3 Trials

rethinkALZ

REducing Tau Hyperphosphorylation and INflammation Kinetically

A 52-week trial of simufilam 100 mg b.i.d or placebo (1:1) in 804 mild-to-moderate AD patients (NCT04994483).

Top-line results of our 52-week Phase 3 trial are expected by year-end 2024.

refocusALZ

REstoring Filamin A's nOrmal [CU] Shape

A 76-week trial of simufilam 50 mg or 100 mg b.i.d or placebo (1:1:1) in 1,125 mild-to-moderate AD patients (NCT05026177).

Top-line results of our 76-week Phase 3 trial are expected approximately mid-year 2025.

# Phase 3 Program Overview

- **Both Phase 3 trials are fully enrolled and on-going, with 1,900+ patients recruited from >150 clinical sites in the U.S., Canada, Puerto Rico, South Korea and Australia.**
  - There is no overlap among our Phase 3 clinical sites, i.e., sites may participate in one P3 or the other, but not both.
  - Premier Research is the independent clinical research organization (CRO).
  - An independent EDC, Signant Health, collects data from clinical trial sites on e-platforms.
  - An independent Data and Safety Monitoring Board (DSMB) monitors patient safety.
  - Board-certified neuroradiologists at Clario, an independent CRO, analyze MRI safety data.
  - p-tau biomarker testing by Neurocode Labs Inc., an independent, CAP-accredited, CLIA-certified laboratory.
- **Both trials have identical co-primary endpoints under Special Protocol Assessments (SPA).**
  - Change in cognition scores on ADAS-Cog12 scale, baseline to end-of-treatment, drug vs placebo.
  - Change in health function scores on ADL scale, baseline to end-of-treatment, drug vs placebo.

# Phase 3 Study Program

## 52 Weeks – Two Arms

rethinkALZ

804 Patients  
Randomized (1:1)

simufilam 100 mg b.i.d.

matching placebo b.i.d.

## 76 Weeks – Three Arms

refocusALZ

1,125 Patients  
Randomized (1:1:1)

simufilam 50 mg b.i.d.

simufilam 100 mg b.i.d.

matching placebo b.i.d.

Optional for patients  
who complete a  
Phase 3 trial.

## Open-label Study

simufilam 100 mg b.i.d.  
Planned for up to 3 years

# Phase 3 Study Endpoints

rethinkALZ

804 Patients  
Randomized (1:1)

52 Weeks – Two Arms

simufilam 100 mg b.i.d.

matching placebo b.i.d.

Efficacy Outcomes, Both Trials:

ADAS-Cog12 (Cognition)

ADCS-ADL (Health Function)

*iADRS (Composite of Cognition + Function)*

refocusALZ

1,125 Patients  
Randomized (1:1:1)

76 Weeks – Three Arms

simufilam 50 mg b.i.d.

simufilam 100 mg b.i.d.

matching placebo b.i.d.

Sub-studies:

Plasma biomarkers

CSF biomarkers

Amyloid PET

Tau PET

Volumetric MRI

ReFOCUS only

*ADAS-Cog = The Alzheimer's Disease Assessment Scale – Cognitive Subscale.*

*ADCS-ADL = Alzheimer's Disease Cooperative Study – Activities of Daily Living.*

*iADRS = integrated Alzheimer's Disease Rating Scale, a composite measure of ADAS-Cog and ADCS-ADL.*

# Key Eligibility Criteria

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- **Age 50-87**
- **Clinical Stage 4 or 5 of the Alzheimer's continuum (NIA/AA criteria 2018)**
- **MMSE  $\geq 16$  and  $\leq 27$**
- **CDR-Global Score of 0.5, 1 or 2**
- **Elevated plasma p-tau181 or prior evidence of AD pathology by PET or CSF**
- **Background AD medications stable for 12 weeks prior to randomization**
- **Not more than 2 doses of anti-amyloid antibodies**
- **Other inclusion/exclusion criteria**

# Preliminary Baseline Characteristics

	ReTHINK (n=797)	ReFOCUS (n=1,123)
Mild AD (N,%)	569, 71.4%	797, 71.0%
APOE ε4 carrier (N,%)	472, 59.2%	645, 57.4%
One APOE ε4 allele (N,%)	383, 48.1%	529, 47.1%
ε4 homozygotes (N,%)	89, 11.2%	116, 10.3%
AChEI and/or memantine use for AD symptoms (N,%)	508, 63.7%	627, 55.8%
MMSE (mean, SD)	21.7 (3.2)	22.0 (3.5)
ADAS-Cog12 (mean, SD)	25.1 (8.7)	24.7 (9.5)
ADCS-ADL (mean, SD)	65.0 (9.2)	65.4 (9.2)
CDR – Global (mean, SD)	0.79 (0.36)	0.75 (0.3)
CDR – SB (mean, SD)	4.7 (2.2)	4.31 (2.1)

*Note: Preliminary baseline characteristics are for the interim safety analysis set and may differ in the final dataset.*

# Plasma P-tau181 Assay

**Plasma p-tau181 was the sole qualifier of AD pathophysiology in both Phase 3 trials.\***

Elevated levels of p-tau is believed to be predictive and specific assay of Alzheimer's neuropathology.



\*Unless patients had pre-existing PET or CSF biomarkers confirming AD pathology

# Current Enrollment Trends

- **1,900+ patients with mild-to-moderate AD are randomized into the Phase 3 trials.**
  - 635 patients completed the 52-week RETHINK-ALZ study. All patients have completed treatment
  - Over 550 patients have completed the 76-week REFOCUS-ALZ study at November 7, 2024
  - 21% dropout rate 52-week RETHINK-ALZ study
  - ~ 25% dropout rate in 76-week REFOCUS-ALZ ; expected to increase
  - Over 1,185 completers in both Phase 3 trials at November 7, 2024
  - ~ 90% of Phase 3 patients are recruited from clinical sites in the U.S. and Canada
- **~ 70% of Phase 3 patients entered the study with mild AD (MMSE 20-27).**
- **~ 88% of patients who've completed a P3 trial have opted to enter the open-label ext. study.**
- **Last patient visit completed for the 52-week trial; Expected May 2025 for the 76-week trial.**

# Drug Safety – Interim Data

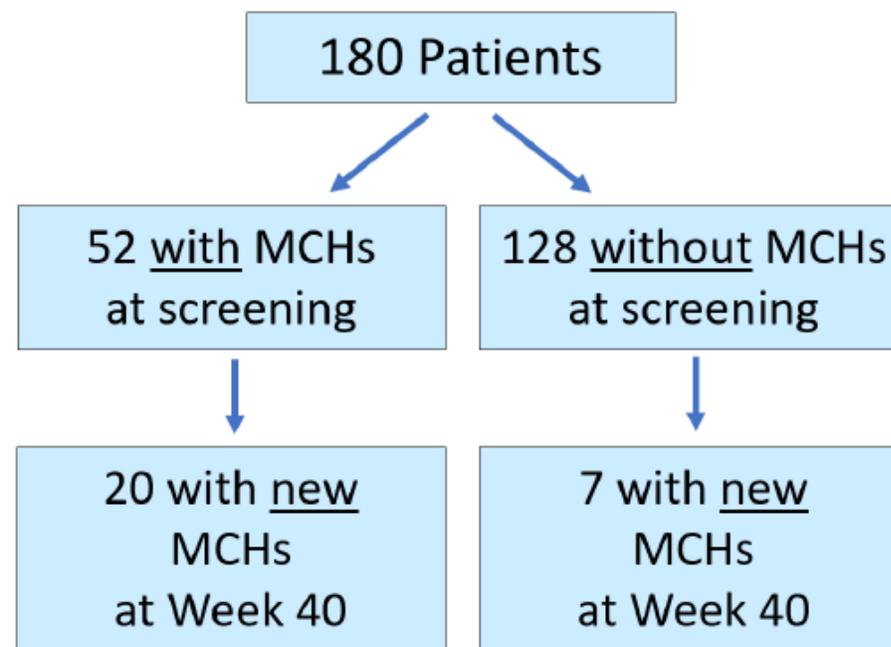
- **Adverse events to date have been typical for an elderly age group.**
  - Covid-19 and urinary tract infections appear to be most frequent adverse events in Phase 3 trials.
  - Final drug safety data are expected at the conclusion of the Phase 3 program.
- **The Data and Safety Monitoring Board (DSMB) is composed of independent clinical research experts who periodically review interim patient safety data.**
  - Routine, scheduled DSMB meetings were held September 2024, March 2024 and September 2023.
  - Each meeting recommended that the Phase 3 trials continue as planned, without modification.

# Interim Phase 3 Safety Data on ARIA

A key risk associated with anti-amyloid antibody drugs is amyloid related imaging abnormalities, or ARIA, which can be serious.

Blinded, interim MRI safety analysis suggests simufilam is NOT associated with treatment-emergent ARIA.

- Week-40 MRIs were examined by outside experts for 180 of 222 Alzheimer's patients enrolled in our 76-week Phase 3 study ('volumetric MRI sub-study').
- ARIA-E was not observed in any patient.
- ARIA-H (microhemorrhages or MCHs) was a common finding at screening (29%).
- Incidence of new ARIA-H was similar to other placebo reports.
- 85% of patients did not develop new MCHs.



# Top-line Results Expected by Year-end 2024

## rethinkALZ

- Last patient visit completed.
- Top-line results on efficacy expected by year-end 2024.

## refocusALZ

- Last patient visit expected by May 2025.
- Top-line results on efficacy expected approximately mid-year 2025.

*The statistical analysis plan (SAP) for RethinkALZ has been finalized. The SAP for RefocusALZ to be prospectively defined, documented and finalized prior to unblinding of RefocusALZ data.*

# Open-label Extension Study

- Study provides no-cost access to oral simufilam to Alzheimer's patients who have successfully completed a Phase 3 study of simufilam and who meet other entry criteria for up to 1 year.

## July 2024 Changes

- We announced intention to extend the Phase 3 open-label extension trial.
- Open-label extension can continue for up to 36 months or until a new drug application for simufilam has been reviewed by FDA.
- Offers a bridge for any gap between patients ending treatment in a clinical trial and the Company reporting to regulatory authorities the results of the ongoing, randomized, placebo-controlled Phase 3 trials.
- Plans to add cognition and plasma biomarker monitoring to the open-label extension trial in order to gather additional long-term data on the potential impact of simufilam treatment.

# Intellectual Property

- **Simufilam is a novel molecule. Cassava Sciences owns exclusive, worldwide rights to simufilam, diagnostic assets and related technologies, without royalty obligations to any third party.**
- **Our patent protection includes nine issued U.S. patents covering simufilam, its solid forms, and uses of simufilam for Alzheimer’s disease and other neurodegenerative diseases, as well as other novel filamin-binding molecules.**
- **Issued U.S. patents with respect to simufilam have terms expiring on dates ranging from 2029 to 2040, subject to any patent extensions that may be available for such patents. Corresponding foreign filings have been made for each U.S. filing.**
- **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**

# Financial Snapshot

Nasdaq ticker: SAVA

Shares Outstanding  $\approx$  48.1 million

## Unaudited Financials at September 30, 2024

Cash & Cash Equivalent Balance  $\approx$  \$149.0 million

Restricted Cash \$ 40.0 million

Debt or Warrants Outstanding none

*Cash Use for Operations for 2nd Half 2024 is expected to range from \$40 - \$50 million, plus a legal settlement of \$40 million (held in Restricted Cash).*

# Thank you!

