We Focus on Alzheimer’s disease

September 13, 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 clinical results of our open-label or CMS study 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. In addition, 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. Also, our interim data and analysis should not be relied upon as predictive of full study results for the open-label study, or any other study. You should not place undue reliance on these statements or any scientific data we present or publish.

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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

Nadav Friedmann, PhD/MD - CMO, Board member
Eight 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

Lindsay H. Burns, PhD - SVP Neuroscience

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

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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Richard Barry
Founding Partner, Portfolio Manager, Eastbourne Capital

Michael O'Donnell
Partner, Orrick LLP
• 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.

• We are developing simufilam, a drug candidate for the proposed treatment of Alzheimer's disease.

• Simufilam is a proprietary, oral drug, developed in-house with academic collaborators.

• We are now conducting Phase 3 studies with simufilam in patients with Alzheimer’s disease dementia.

• Science programs were 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

Over 500 Patients Are Now Enrolled in Our Phase 3 Program

Phase 3 Program

- Two on-going Phase 3 studies in patients with Alzheimer’s disease dementia.
  - Patients are being screened in clinical trial sites in the U.S., Puerto Rico, Canada, S. Korea and Australia.
  - 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.

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 Q4 2022.
  - Our goal is to announce top-line clinical results for this study approximately year-end 2022.

- Randomized, placebo-controlled Cognition Maintenance Study (CMS) in Alzheimer’s patients.
  - Target enrollment: over 100 subjects.
  - Over 50% have completed this study.
  - All clinical data remains blinded.
  - Our goal is to complete enrollment for the CMS study in Q4 2022 and to announce data approximately third-quarter 2023.
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 β42 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, disables A β42 signaling via α7nAChR and TLR4.

Through a single target, simufilam reduces neurodegeneration and neuroinflammation.
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.
## Summary of Preclinical Effects

<table>
<thead>
<tr>
<th>Simufilam</th>
<th>Intracerebro-ventricular (ICV) Aβ_{42} infusion mouse model</th>
<th>Triple transgenic AD mouse model</th>
<th>Post-mortem human AD brain tissue</th>
<th>Post-mortem human age-matched control brain tissue treated with Aβ_{42} in vitro</th>
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<tbody>
<tr>
<td>Reduced FLNA linkage to α7nAChR/TLR4</td>
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<tr>
<td>Reduced Aβ_{42} bound to α7nAChR</td>
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<td>√</td>
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<tr>
<td>Reduced amyloid deposits and NFTs</td>
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<tr>
<td>Reduced tau hyperphosphorylation</td>
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<tr>
<td>Improved function of α7nAChR, NMDAR and insulin receptors</td>
<td>√</td>
<td>√</td>
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<tr>
<td>Improved synaptic plasticity (activity-dependent Arc expression)</td>
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<td>Reduced inflammatory cytokine levels</td>
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<td>Improved cognition/behavior</td>
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Simufilam is a disease-modifying drug for Alzheimer’s disease dementia that also provides symptomatic improvement.

Evaluate safety, biomarkers and cognition in a randomized, placebo-controlled study of simufilam.
Phase 2b - Study Design

Objective

Patient Enrollment

- Mild-to-moderate Alzheimer’s, MMSE ≥16 to 26
- Key Inclusion Criterion: CSF Total tau/\(A\beta_{42}\) ≥ 0.28
- Sixty (64) patients recruited across 9 study sites in the U.S.

Study Design

Baseline Cognition Test

1:1:1 Randomization

28-Day Treatment Period

- Simufilam 50 mg oral, twice-daily
- Simufilam 100 mg oral, twice-daily
- Matching placebo

2nd CSF Draw & Cognition Test

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

% Change - Baseline to Day 28

-55% -55%
-50%
-45%
-40%
-35%
-30%
-25%
-20%
-15%
-10%
-5%
0%
5%
10%
15%
20%
25%
30%
35%
40%
45%
50%
55%

- Placebo
- 50 mg
- 100 mg

+p < 0.05, †p < 0.01, # p ≤ 0.001, *p < 0.0001 vs. placebo
Phase 2b Results – Patient Responder Analysis

% of Patients Who Responded to Simufilam on CSF Biomarkers

- **Tau/p-Tau Biomarkers**: 98%
- **Biomarkers of Neuroinflammation**: 98%
- **Biomarkers of Neurodegeneration**: 98%
- **Biomarkers of BBB Integrity**: 95%
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 dementia 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.

- 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.
  - Simufilam appears safe and well-tolerated to date.

- In August 2022, we announced top-line safety & cognitive results of the first 100 evaluable patients who completed 12 months of open-label treatment with simufilam 100 mg twice-daily.
  - 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.
An interim analysis was conducted on the first 100 evaluable patients who completed at least 12 months of open-label treatment with simufilam 100 mg twice daily.

Top-line results of this interim analysis show that from baseline to month-12:

- Drug appears safe and well tolerated.
- Overall ADAS-Cog11 scores improved an average of 1.5 points (S.D. ± 6.6; P<0.05)
- 63% of the 100 patients showed an improvement in ADAS-Cog11 scores, and this group of patients improved an average of 5.6 points (S.D. ± 3.8).
- An additional 21% of the 100 patients declined less than 5 points on ADAS-Cog11, and this group of patients declined an average of 2.7 points (S.D. ± 1.4).

All clinical data from our open-label study are inherently exploratory in nature and, as with all open-label data, should be interpreted with caution. Data results from our open-label study does not constitute, and should not be interpreted as, evidence of therapeutic benefit for simufilam.
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:**

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

P < 0.00001 for all by paired t test.
Not shown: CSF Aβ₄₂ increased significantly (+84%), as expected.
Goal is to compare cognition in ≈ 100 AD patients who continue vs. discontinue simufilam treatment over 6 months, following 1-year open-label treatment.

CMS was initiated May 2021. As of August 2022, 50 subjects have completed this study. Our goal is to announce study results approximately Q3 2023.
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).

As of September 13, 2022, >500 patients were enrolled in our Phase 3 studies.

### 1st Phase 3
- **Enrollment Target**: ~ 750 Subjects
- **Simufilam Treatment**: 100 mg
- **Length of Treatment**: 52-weeks

### 2nd Phase 3
- **Enrollment Target**: ~ 1,000 Subjects
- **Simufilam Treatment**: 100 mg or 50 mg
- **Length of Treatment**: 76-weeks

### Co-Primary Endpoints
- **Cognition Scale**: ADAS-Cog12
- **Function Scale**: ADCS-ADL

### Secondary Endpoints
- **Cognition + Function Scale**: iADRS
- **Dementia-related Behavior Scale**: NPI₁₂

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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
Phase 3 Studies in Alzheimer’s disease

➢ 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.

- SavaDx is an early-stage product candidate, benefiting from long-term scientific & financial support from NIH.

- Working with third parties, we continue to evaluate an innovative method to detect FLNA without the use of antibodies.

- SavaDx is our lower priority program as compared to simufilam.
**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 over six issued patents. These currently run beyond 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 | ≈ 40.1 million |

<table>
<thead>
<tr>
<th>Financials at June 30, 2022</th>
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<tr>
<td>Cash Balance</td>
<td>≈ $197.2 million</td>
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<tr>
<td>Debt</td>
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</table>

*Est. Cash Use for Operations in the 2nd Half of 2022 is Approximately $45 to $55 million, Depending on Rate of Patient Enrollment and Other Expenses.*
Thank you!
Appendix: Key Publications

**Journal of Prevention of Alzheimer’s Disease**
2020; DOI: 10.14283
**PTI-125 Reduces Biomarkers of Alzheimer’s Disease In Patients:**

**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:**

**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.