Sumifilam Significantly Improves Eleven CSF Biomarkers in a Randomized, Placebo-controlled, One-month Clinical Trial in Alzheimer’s Disease Patients

Lindsay BURNS, Hoau-Yan WANG, Zhe PEI, Kuo-Chieh LEE, Yaneicy GONZALEZ-ROJAS, Tamara DOEHNER, John PUENTE, Patrick SCIARA, Brian BECK, Evelyn LOPEZ-BRIGNONI, Boris NIKOLOV, Carrie CROWLEY, Nadav FRIEDMANN

November 7, 2020
Forward-Looking Statements

This presentation contains “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995. To identify such forward-looking statements, in some cases we use terms such as “predicts,” “believes,” “potential,” “estimates,” “anticipates,” “expects,” “plans,” “intends,” “may,” “could,” “might,” “should” or other words that will convey risk or uncertainty of future events or outcomes. All statements other than statements of historical fact contained in this presentation including, but not limited to, statements regarding plans or timing for future Phase 3 clinical studies with sumifilam; the interpretation of prior or current results of our Phase 2 clinical studies, including the measured effects of sumifilam on cognition; plans to publish results in a peer-reviewed journal; potential health benefits, if any, of changes in levels of CSF biomarkers; verbal commentaries made by Cassava Sciences’ employees; and potential benefits, if any, of the Company’s product candidates for Alzheimer’s disease are forward-looking statements.

Such statements are based largely 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, the severity and duration of health care precautions given the international outbreak of an infectious disease and including those described in the section entitled “Risk Factors” in our Annual Report on Form 10-K for the year ended December 31, 2019 and future reports to be filed with the SEC. In light of these risks, uncertainties and assumptions, forward-looking statements and events discussed in this presentation are inherently uncertain and may not occur. Actual results could differ quickly, materially and adversely from those anticipated or implied in the forward-looking statements. Accordingly, you should never rely upon forward-looking statements as predictions of future events. We do not undertake any obligation to update this corporate presentation or any forward-looking statements included therein, except as required by law.

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

- Sumifilam is under clinical development by Cassava Sciences, Inc.
- L.H. Burns, PhD, N. Friedmann, PhD, MD, and C. Crowley are employees of Cassava Sciences.
- H-Y. Wang, PhD, is a consultant to Cassava Sciences.
- H-Y. Wang, PhD, Z. Pei, PhD, and K-C. Lee are employees of City University of New York School of Medicine.
- Sumifilam benefits from long-term scientific & financial support from the National Institute on Aging (AG050301, AG056166, AG060878, AG065152).
Introduction to Sumifilam

- Sumifilam is a proprietary, small molecule drug candidate to treat Alzheimer’s disease (AD) and other neurodegenerative diseases.
  - Drug was discovered and developed in-house, 2008 to present.

- Sumifilam binds a single target, has a dual mechanism of action:
  - Reduces neurodegeneration and neuroinflammation.
  - Published preclinical and mechanism of action data support sumifilam’s potential as a disease-modifying drug for AD that may also enhance cognition.
Sumifilam: A Journey of Basic Research to Clinical Research

1. <2008
   Basic research around neurobiology of Filamin A (FLNA).

2. 2009
   Discovery that altered FLNA associates with $\alpha_7n$AChR when $\text{A}\beta$ signals.

3. 2010
   Screening/testing of compounds that bind altered FLNA and block $\alpha_7n$AChR/$\text{A}\beta$ interaction.

4. 2011
   Sumifilam (formerly, PTI-125) binds altered FLNA with high affinity, blocks $\alpha_7n$AChR/$\text{A}\beta$ interaction.
   Preclinical testing of sumifilam.

5. 2017 - present
   Clinical testing of sumifilam.
   Positive results reported in Alzheimer’s patients.
Phase 2b Clinical Study of Sumifilam

I. Mechanism of Action

II. Phase 2b Study Results

III. Study Conclusions
Target of Sumifilam is *Altered* Filamin A (FLNA)

FLNA is an intracellular scaffolding protein anchored in the cell membrane. FLNA interacts with > 90 proteins, influencing many signaling pathways.

The AD brain carries an *ALTERED* conformation of FLNA. Altered FLNA is critical to amyloid beta’s toxicity.
Sumifilam Mechanism of Action

• Altered FLNA enables $\text{A}_\beta_{42}$ signaling via two different receptors:

  1) $\alpha_7$-nicotinic acetylcholine receptor ($\alpha_7\text{nAChR}$) → hyperphosphorylates tau

  2) Toll-like receptor 4 (TLR4) → releases inflammatory cytokines

• Sumifilam preferentially binds altered FLNA, restores its proper shape/function, potently suppressing $\text{A}_\beta_{42}$ signaling via $\alpha_7\text{nAChR}$ and TLR4.

• Through a single target, sumifilam reduces both neurodegeneration and neuroinflammation.
Altered FLNA links to α7-nicotinic acetylcholine receptor

- Aβ_{42} binds α7nAChR and recruits FLNA, altering its shape.
- Altered FLNA linkage to α7nAChR enables a *femtomolar* affinity of Aβ_{42} for α7nAChR and the signaling that hyperphosphorylates tau.

Sumifilam binds altered FLNA, restores its normal shape, stops Aβ_{42} signaling and tau hyperphosphorylation.
Altered FLNA links to α7-nicotinic acetylcholine receptor

- $\text{A}\beta_{42}$ binds $\alpha7$nAChR and recruits FLNA, altering its shape.

- Altered FLNA linkage to $\alpha7$nAChR enables a femtomolar affinity of $\text{A}\beta_{42}$ for $\alpha7$nAChR and the signaling that hyperphosphorylates tau.

Sumifilam binds altered FLNA, restores its normal shape, stops $\text{A}\beta_{42}$ signaling and tau hyperphosphorylation.
Altered FLNA links to toll-like receptor 4 (TLR4)

• Altered FLNA linkage to TLR4 enables Aβ_{42} to activate TLR4.

• Persistent TLR4 activation results in chronic neuroinflammation.
Altered FLNA links to toll-like receptor 4 (TLR4)

- Altered FLNA linkage to TLR4 enables $\alpha_\beta_{42}$ to activate TLR4.

- Persistent TLR4 activation results in chronic neuroinflammation.

*Sumifilam binds altered FLNA, restores its normal shape, stops $\alpha_\beta_{42}$-induced neuroinflammation.*
### Summary of Preclinical Effects

<table>
<thead>
<tr>
<th>Sumifilam</th>
<th>Intracerebroventricular (ICV) Aβ_{42} infusion mouse model</th>
<th>Triple transgenic AD mouse model</th>
<th>Postmortem human AD brain tissue</th>
<th>Postmortem human age-matched control brain tissue treated with Aβ_{42} in vitro</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced FLNA linkage to α7nAChR/TLR4</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Reduced Aβ_{42} bound to α7nAChR</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Reduced amyloid deposits and NFTs</td>
<td>√</td>
<td>√</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Reduced tau hyperphosphorylation</td>
<td>√</td>
<td>√</td>
<td>–</td>
<td>√</td>
</tr>
<tr>
<td>Improved function of α7nAChR, NMDAR and insulin receptors</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Improved synaptic plasticity (activity-dependent Arc expression)</td>
<td>–</td>
<td>√</td>
<td>–</td>
<td>√</td>
</tr>
<tr>
<td>Reduced inflammatory cytokine levels</td>
<td>√</td>
<td>√</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Improved cognition/behavior</td>
<td>–</td>
<td>√</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>
Phase 2b Clinical Study of Sumifilam

I. Mechanism of Action

II. Phase 2b Study Results

III. Study Conclusions
Clinical Hypothesis

Published preclinical effects and mechanism of action suggest sumifilam is a disease-modifying drug for AD and may enhance cognition.

Phase 2b Study Objective

Evaluate safety, biomarkers and cognition in a well-controlled study of sumifilam.
Phase 2b Study Design
Randomized, placebo-controlled, multi-center, multi-dose study.

**Screening**
- Mild-to-moderate AD, age 50-85
- MMSE ≥16 and ≤26

**Key Inclusion Criterion:**
- CSF Total tau/Aβ$_{42}$ ≥ 0.28

Sixty (64) patients recruited across 9 sites in the US

**Day 1**
- Baseline Cognition Test

**28-Day Treatment Period**
- Sumifilam 50 mg oral, twice daily
- Sumifilam 100 mg oral, twice daily
- Matching placebo, twice daily

**Day 28**
- CSF Draw & Cognition Test

**Primary Endpoint:** Biomarkers of disease

**Secondary Endpoint:** Cognition
Phase 2b – Safety

• Sumifilam was well-tolerated
• No serious adverse events
• No drug-related patient discontinuation
• No drug-related adverse events
  • Common, non-persistent AEs observed in both placebo & drug groups.
Phase 2b Results – CSF Total Tau and P-Tau181 Decreased

Total Tau

P-Tau181

<table>
<thead>
<tr>
<th>Change - Baseline to Day 28</th>
<th>Total Tau</th>
<th>P-Tau181</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-15%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-25%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Placebo
50 mg
100 mg

#p ≤ 0.001, *p < 0.0001 vs. placebo
Phase 2b Results – CSF Aβ_42, Low in AD, Increased

![Graph showing change in CSF Aβ_42 from baseline to day 28 for Placebo, 50 mg, and 100 mg groups. The graph indicates a significant increase in the 50 mg group compared to Placebo, with p = 0.0015, and a trend in the 100 mg group, with p = 0.0003 vs. Placebo.](image-url)
Phase 2b Results - Neurodegeneration Biomarkers in CSF Decreased

Neurogranin

-50%
-40%
-30%
-20%
-10%
0%

Change - Baseline to Day 28

Placebo
50 mg
100 mg

Neurofilament Light Chain

-50%
-40%
-30%
-20%
-10%
0%

+p = 0.048, #p = 0.001,
*p < 0.0001 vs. placebo
Phase 2b Results - Neuroinflammation Biomarkers in CSF Decreased

**YKL-40**
- Placebo: -60%
- 50 mg: -50%
- 100 mg: -40%

**IL-6**
- Placebo: -30%
- 50 mg: -20%
- 100 mg: 0%

**sTREM2**
- Placebo: -20%
- 50 mg: 0%
- 100 mg: 10%

Visual representation:
- Placebo: Gray bars
- 50 mg: Orange bars
- 100 mg: Brown bars

Legend:
- †: p < 0.01
- #: p ≤ 0.001 vs. placebo

Graph shows change from baseline to Day 28 for YKL-40, IL-6, and sTREM2 biomarkers.
Elevated Levels of HMGB1 Trigger Loss of Neurons

- **High-Mobility Group Box 1 (HMGB1)** is a pathogenic protein that induces neuroinflammation, neurite degeneration and cell death.
  - Actively secreted by glia; released by necrotic cells.
  - Induces cytokine production, activates immune cells, stimulates auto-antibodies, regulates gene transcription.
  - Described as a ‘danger molecule.’
- **HMGB1** elevated in AD, other diseases of neuroinflammation and neuronal loss.
- **HMGB1** activates TLR4 and Receptor for Advanced Glycation End products (RAGE).
Phase 2b Results – CSF HMGB1 Decreased

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Change - Baseline to Day 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-40%</td>
</tr>
<tr>
<td>50 mg</td>
<td>-30%</td>
</tr>
<tr>
<td>100 mg</td>
<td>-20%</td>
</tr>
</tbody>
</table>

# p < 0.001 vs. placebo
Phase 2b Results - BBB Integrity Improved

<table>
<thead>
<tr>
<th>% Change - Baseline to Day 28</th>
<th>CSF Albumin</th>
<th>CSF Immunoglobulin G</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline to Day 28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 mg</td>
<td>+p &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>100 mg</td>
<td></td>
<td>+p = 0.0002 vs. placebo</td>
</tr>
</tbody>
</table>

Placebo

+ Placebo

- 50 mg

- 100 mg

+p < 0.05

#p = 0.0002 vs. placebo
Phase 2b Summary of Results - CSF Biomarkers

% Change - Baseline to Day 28

-55% -45% -35% -25% -15% -5% 5% 15% 25%

Placebo 50 mg 100 mg

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

• CANTAB (Cambridge Neuropsychological Test Automated Battery) is a widely used, computer-based battery of memory tests sensitive to subtle changes in cognition.
  • Tests are independent of language skills, speed, gender or education.

• Cognitive assessments were made on Day 1 (pre-dose) and again on Day 28.

• Patients were tested on ‘Episodic Memory’ and ‘Spatial Working Memory’.
  • Patients advance through progressively more difficult levels.
  • Outcome measure = total errors, with errors imputed for more difficult levels not reached, so……..

*Lower score is better!
Phase 2b Results - Episodic Memory

Episodic Memory Endpoint:
Lower score is better in Total Errors on Paired Associates Learning (PAL).

![Bar chart showing change in episodic memory from baseline to Day 28 for Placebo, 50 mg, and 100 mg doses.](chart.png)

- Placebo: -1.5
- 50 mg: -5.7
- 100 mg: -4.5

Effect Sizes:
- 37% Effect Size for 50 mg
- 23% Effect Size for 100 mg
Phase 2b Results - Spatial Working Memory

Spatial Working Memory Endpoint:
Lower score is better in Total Errors on Spatial Working Memory task.

Change – Baseline to Day 28

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>50 mg</th>
<th>100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-0.41</td>
<td>-1.65</td>
<td>-3.33</td>
</tr>
</tbody>
</table>

17% Effect Size
46% Effect Size
Phase 2b Results - Cognition/Biomarker Correlation

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

Cognition/Biomarker Correlations ($R^2$)
Phase 2b Results - Target Engagement in Lymphocytes

Reduced FLNA linkages:

- FLNA – α7nAChR
- FLNA – TLR4

Change – Baseline to Day 28

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>50 mg</th>
<th>100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>-5%</td>
<td>-5%</td>
<td>-5%</td>
<td>-5%</td>
</tr>
<tr>
<td>-10%</td>
<td>-10%</td>
<td>-10%</td>
<td>-10%</td>
</tr>
<tr>
<td>-15%</td>
<td>-15%</td>
<td>-15%</td>
<td>-15%</td>
</tr>
<tr>
<td>-20%</td>
<td>-20%</td>
<td>-20%</td>
<td>-20%</td>
</tr>
<tr>
<td>-25%</td>
<td>-25%</td>
<td>-25%</td>
<td>-25%</td>
</tr>
<tr>
<td>-30%</td>
<td>-30%</td>
<td>-30%</td>
<td>-30%</td>
</tr>
<tr>
<td>-35%</td>
<td>-35%</td>
<td>-35%</td>
<td>-35%</td>
</tr>
<tr>
<td>-40%</td>
<td>-40%</td>
<td>-40%</td>
<td>-40%</td>
</tr>
</tbody>
</table>

* p < 0.05, (*) p = 0.076 vs placebo
Phase 2b Results - Summary of Drug Effects

• 98% of patients treated with sumifilam 50 mg or 100 mg b.i.d. for 28 days showed improvements in validated biomarkers of AD pathology; neuroinflammation; and neurodegeneration; with no safety issues.

• Sumifilam appears to enhance cognition.
  • 37% and 23% effect sizes in Episodic Memory vs. placebo
  • 17% and 46% effect sizes in Spatial Working Memory vs. placebo
  • Improved cognition correlated most strongly with reduction in levels of P-tau\textsuperscript{181} (R\textsuperscript{2} = 0.5)

• Target engagement and mechanism of action were demonstrated in this Phase 2b and in prior clinical and pre-clinical studies.
Phase 2b Clinical Study of Sumifilam

I. Mechanism of Action

II. Phase 2b Study Results

III. Study Conclusions
Study Conclusions

• A well-controlled study of sumifilam showed promising treatment effects in mild-to-moderate AD patients.

• Sumifilam improved an entire panel of validated biomarkers of disease, neuroinflammation, and BBB integrity, and appeared to enhance cognition.

• Phase 2b treatment effects replicate prior clinical results and are consistent with published preclinical data and the drug’s mechanism of action.

These data highlight sumifilam’s potential as a disease-modifying treatment for Alzheimer’s disease.
Next Steps

• On-going: *One-year, open-label safety study of sumifilam*
  • Enrolling 100 patients with mild-to-moderate AD, including ADAS-Cog assessments.

• Planned for 2021: *Large-scale safety & efficacy study of sumifilam*

THANK YOU!