Encouraging Interim Results at 9 Months from an Open-Label Study of Simufilam in Patients with Alzheimer's Disease

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

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Disclosures

- The open-label safety study with simufilam is funded by a clinical research grant award from the National Institutes of Health (NIH).
- Simufilam is a proprietary drug candidate of Cassava Sciences, Inc.
- Lindsay Burns, PhD; Nadav Friedmann, PhD, MD; Carrie Crowley; and Antonio Hernandez, PsyD, are employees of Cassava Sciences.
- Hoau-Yan Wang, PhD, Zhe Pei, PhD, and Kuo-Chieh Lee are affiliated with City University of New York School of Medicine. Professor HY Wang is a consultant to Cassava Sciences.
- Clinicaltrials.gov registration # NCT04388254, registered 14 May 2020.

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Open-Label Study of Simufilam

- Simufilam is an oral drug that targets altered filamin A protein in the brain. Restoring the normal shape of filamin A blocks toxic signaling of soluble $A\beta_{42}$.
- We are conducting a multi-center, one-year, open-label study in subjects (N>150) with mild-to-moderate Alzheimer's disease, MMSE ≥ 16 and ≤ 26.
- Outcome measures:
  - Safety
  - Cognition: Alzheimer's Disease Assessment Scale Cognitive subscale (ADAS-Cog11)
  - Behavior: Neuropsychiatric Inventory (NPI)
  - CSF biomarkers: Baseline, 6 months and 12 months

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Interim Analysis

- We conducted a pre-planned interim analysis on the first 50 subjects who completed 9 months of open-label treatment with simufilam 100 mg b.i.d.

- CSF biomarkers were measured in a subset of subjects (N=25) after 6 months of open-label treatment with simufilam.

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Baseline Overview

Simufilam 9-Month Interim Analysis, First 50 Subjects

Attribute	Mean (±SD)
Age (SD)	69 (±6.4)
# Females	23 (46%)
MMSE (SD)	22.6 (±2.9)
ADAS-Cog11 (SD)	16.6 (±7.7)
NPI (SD)	4.7 (±8.2)
# Trial Sites	7

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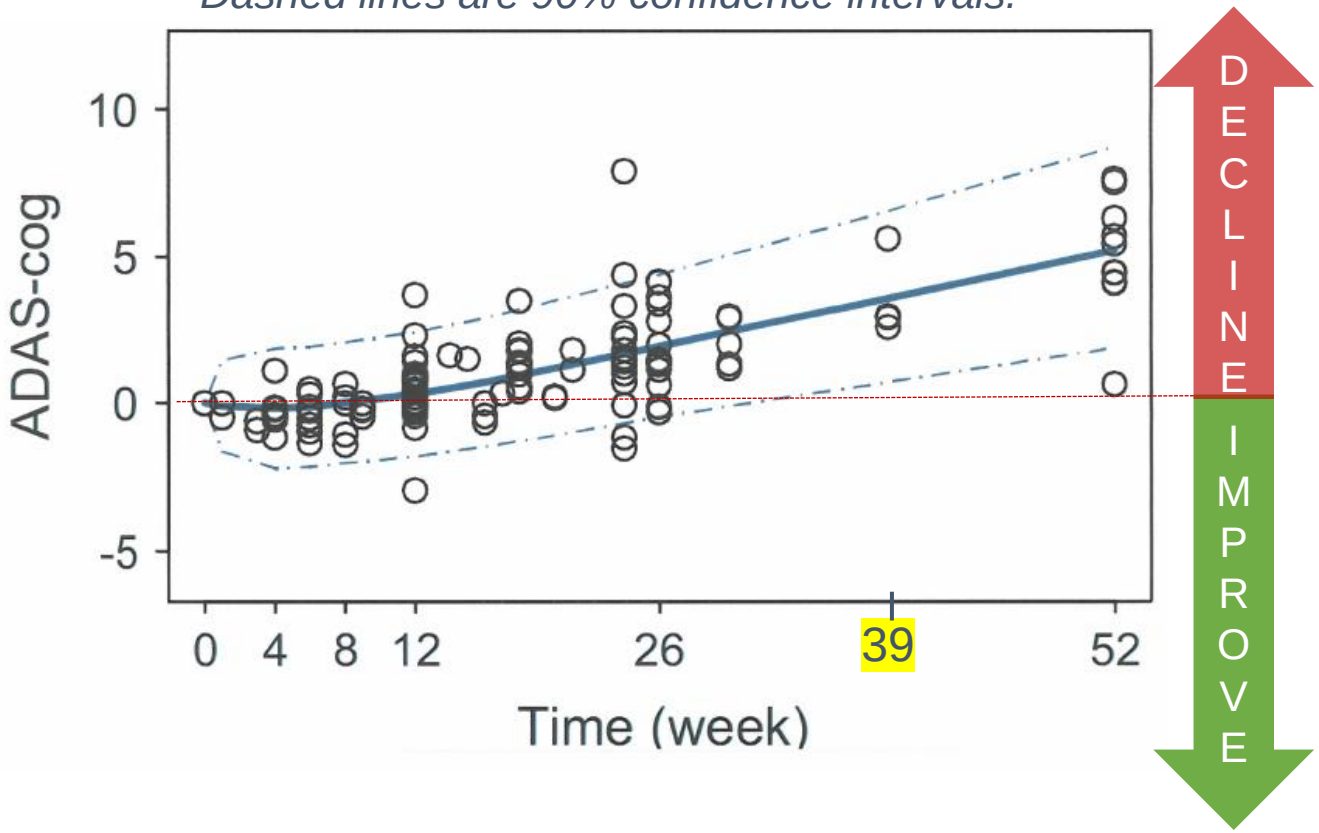
Expected Rate of Cognitive Decline in AD

Meta-analysis Of Placebo Group Decline[1]

Dashed lines are 90% confidence intervals.



- **Cognitive decline was reported in a meta-analysis of 20,000 patients with mild-to-moderate AD[1]:**
  5.5-point decline/year on ADAS-Cog11 in placebo groups.

- **Cognitive decline was reported in two P3 studies of Biogen's aducanumab in patients with early AD[2]:**
  5.2-point decline over 18 months on ADAS-Cog in placebo groups.

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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 Results

ADAS-Cog11 scores improved 3 points at 9 months in the first 50 subjects.

P < 0.001 by paired *t* test: Baseline vs. 9 Months

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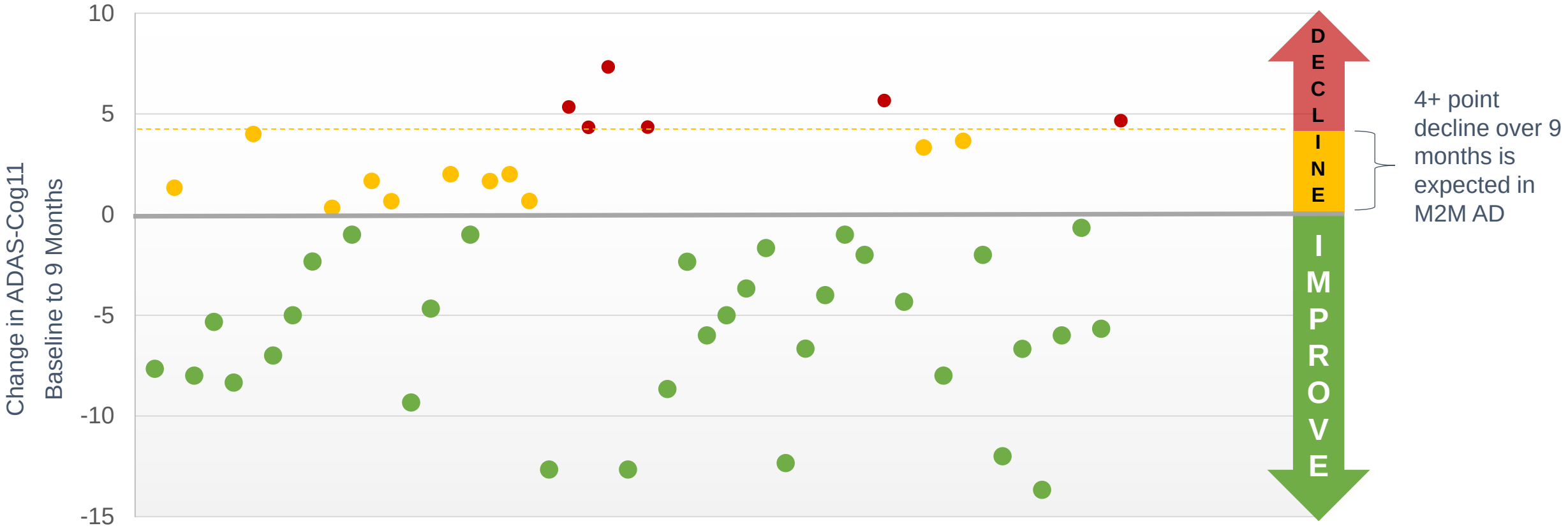
Individual Patient Changes in ADAS-Cog (N=50)

66% of Patients Improved at 9 Months (N=33)
22% of Patients Declined Less Than Expected (N=11)



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CSF Biomarkers

- **Biomarkers of disease were measured in a subset of subjects (N=25) who completed 6 months of simufilam treatment.**
  - Alzheimer's pathology: Amyloid β_{42}, Total Tau and P-tau181
  - Neurodegeneration: Neurogranin and Neurofilament Light Chain (NfL)
  - Neuroinflammation: YKL-40, soluble TREM2 and HMGB1
- **CSF was collected by lumbar puncture at baseline and again at 6 months.**
- **CSF samples were analyzed blind by an outside lab in a 96-well immunoassay (ELISA) format for each biomarker.**

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CSF Biomarkers and Baseline Levels

CSF Biomarker	Significance in AD and MCI	Mean concentration in CSF (pg/mL) ± SD
$A\beta_{42}$	AD pathology, low in CSF	122.8 ± 62.4
Total tau	Marker of neurodegeneration	163.5 ± 33.7
P-tau181	Marker of disrupted tau function	35.7 ± 2.1
Neurogranin	Synaptic loss/degeneration	2,147.6 ± 575.7
Neurofilament Light Chain (NfL)	Axonal loss/degeneration	291.6 ± 55.1
YKL-40	Marker of neuroinflammation	250.4 ± 35.8
sTREM2	Microglial-induced neuroinflammation	1,165.8 ± 421.2
HMGB1	Pathogenic “danger” molecule	722.6 ± 98.6

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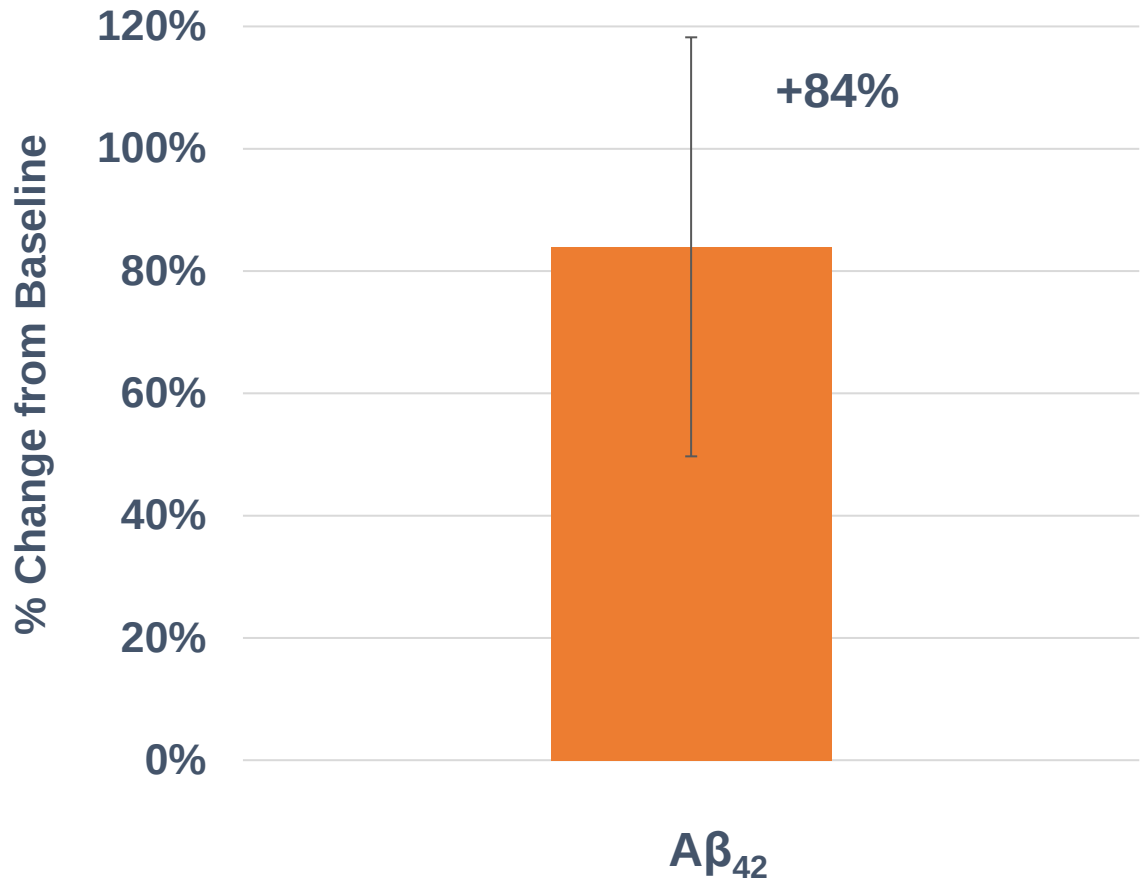
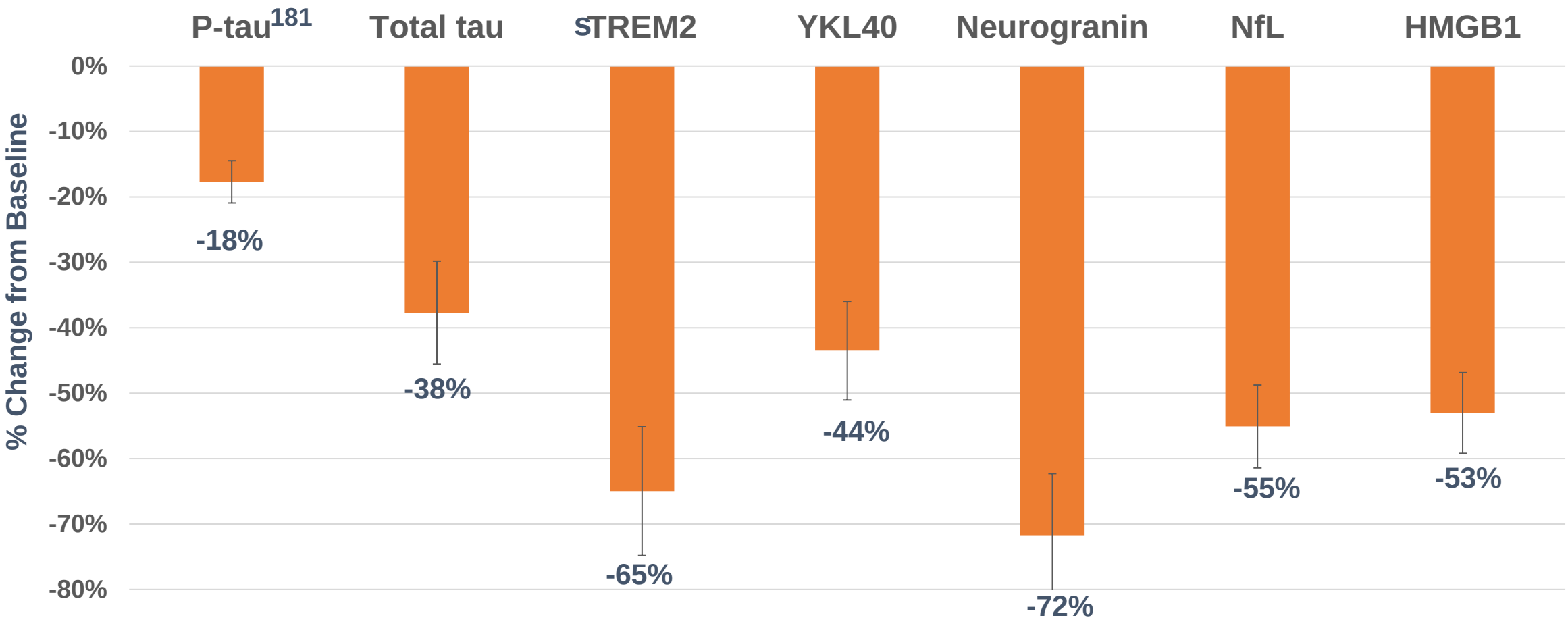
CSF Amyloid-β_{42}

CSF $A\beta_{42}$ increased significantly after 6 months of simufilam treatment.



P < 0.00001 by paired *t* test

Significant Decreases in CSF Biomarkers at Month 6



P < 0.00001 for all by paired *t* test

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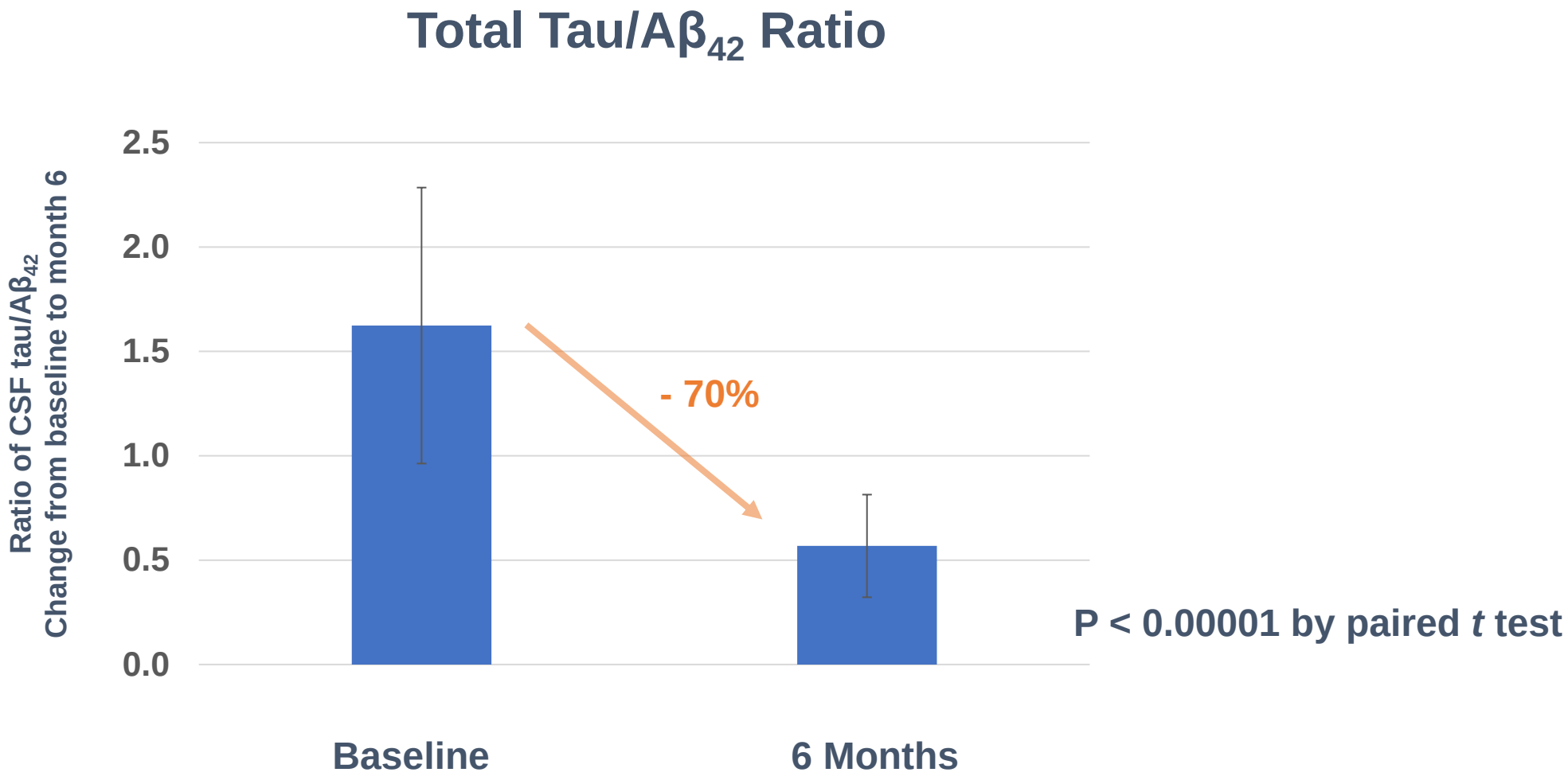
Diagnostic Criterion for AD Decreased Significantly



Improved Behavior Disorders

- Alzheimer's is often accompanied by behaviors disorders, such as anxiety, agitation or delusions, that may become more frequent as disease progresses.
- At baseline, 34% of patients had no neuropsychiatric symptoms on the Neuropsychiatric Inventory (NPI) scale.
- At Month 9, >50% of patients had no neuropsychiatric symptoms on NPI.

Study Timeline	NPI Scale
Baseline	No neuropsychiatric symptoms in 34% of patients
6 months	No neuropsychiatric symptoms in 38% of patients
9 months	No neuropsychiatric symptoms in >50% of patients

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No Safety Issues

- **Simufilam was safe and well-tolerated through 9 months of open-label treatment.**
- **No drug-related serious adverse events.**
- **Non-persistent side-effects commonly found in an elderly population are observed.**
- **<10% dropout rate.**

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Summary of 9-Month Open-Label Simufilam

- Cognition scores improved significantly ($p<0.001$) in patients with mild-to-moderate Alzheimer's disease after 9 months of open-label simufilam.
- Biomarker levels improved significantly (all $p<0.00001$) in patients with mild-to-moderate Alzheimer's disease after 6 months of open-label simufilam.
- Interim analysis data are consistent with prior clinical results, published preclinical data and mechanism of action.

Alzheimer's is a progressive disease that worsens over time. Improvements in cognition, biomarkers and behavior at 9 months suggest highly encouraging treatment effects.

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Next Steps with Simufilam

- A 12-month interim analysis of the open-label study is expected Q4 2021.
- A randomized, controlled trial with simufilam is currently recruiting 100+ subjects with mild-to-moderate Alzheimer's disease.
- A Phase 3 program with simufilam is scheduled for initiation Fall 2021.
  - Two randomized, controlled trials (12 months & 18 months).
  - Total target enrollment ~ 1,750 subjects with mild-to-moderate AD.

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THANK YOU!

- We thank patients who participated in this open-label study.
- We thank the Alzheimer's Association for this opportunity to present our clinical data with simufilam.
- We are grateful for the participation of clinical investigators and researchers Tamara Doehner, John Puente, Brian Beck, Yaneicy Gonzalez Rojas, Evelyn Lopez-Brignoni, Boris Nikolov, Hoau-Yan Wang and Zhe Pei and new investigators who support this study.
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