Interim Results of an Open-label Study of Simufilam in Mild-to-Moderate Alzheimer's Disease

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INTRODUCTION

Simufilam is a small molecule drug candidate for Alzheimer's disease (AD). Simufilam reverses an altered conformation of filamin A in the AD brain, reducing tau hyperphosphorylation and neuroinflammation initiated by $A\beta_{42}$.[1-3] In a prior randomized, placebo-controlled trial in mild-to-moderate AD, oral simufilam significantly improved eleven CSF biomarkers of AD pathology, neurodegeneration, neuroinflammation and blood-brain barrier integrity over 28 days, with no safety issues.

OBJECTIVES

To assess the long-term safety and tolerability of simufilam 100 mg twice-daily for 12 or more months in subjects with mild-to-moderate AD. Another study objective is to measure changes in cognition using ADAS-Cog11 and dementia-related behavior using the Neuropsychiatric Inventory (NPI).

STUDY DESIGN

This open-label study continues to enroll AD patients MMSE ≥ 16 and ≤ 26, and who meet other entry criteria. Study subjects receive 100 mg twice-daily oral simufilam for 12 or more months. Over 200 subjects are now enrolled across 16 investigator sites across the U.S. and Canada. Interim analyses were pre-planned on the first 50 subjects to reach 6, 9 and 12 months of open-label treatment. The study's overall drop-out rate is under 10%.

12-MONTH INTERIM ANALYSIS – Baseline Attributes

Baseline attributes of the first 50 subjects to reach 12 months of treatment are shown below.

Attribute	Baseline Mean (± SD)
Age (SD)	69.6 (±6.4)
# Females	23 (46%)
MMSE (SD)	22.7 (±2.8)
ADAS-Cog11 (SD)	16.7 (±7.86)
NPI (SD)	4.7 (±8.2)
# Trial Sites	7

12-MONTH INTERIM ANALYSIS – Safety

Simufilam is well-tolerated. There are no drug-related serious adverse events through the 12-month interim analysis.

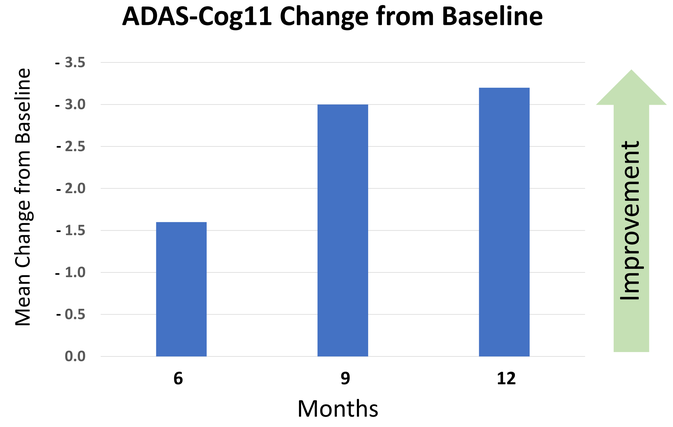
12-MONTH INTERIM ANALYSIS – Cognition

In the first 50 subjects to complete 12 months of open-label treatment with simufilam (negative indicates improvement):

- ADAS-Cog11 improved -3.23 points (mean) from baseline (SD ± 6.25; p<0.001). The median change was -4.0 points.
- 68% of study subjects improved on ADAS-Cog11 from baseline to Month 12 (mean -6.8; SD ± 3.8).
- ADAS-Cog11 scores on Day 1 (mean 16.73 ± 7.86) were significantly different (p<0.001 by paired *t* test) from ADAS-Cog11 scores on Month 12 (mean 13.51 ± 9.20).

Fig 1 shows changes in ADAS-Cog11 scores for the first 50 study subjects to complete 6, 9 and 12 months of treatment.

1



12-MONTH INTERIM RESULTS – NPI

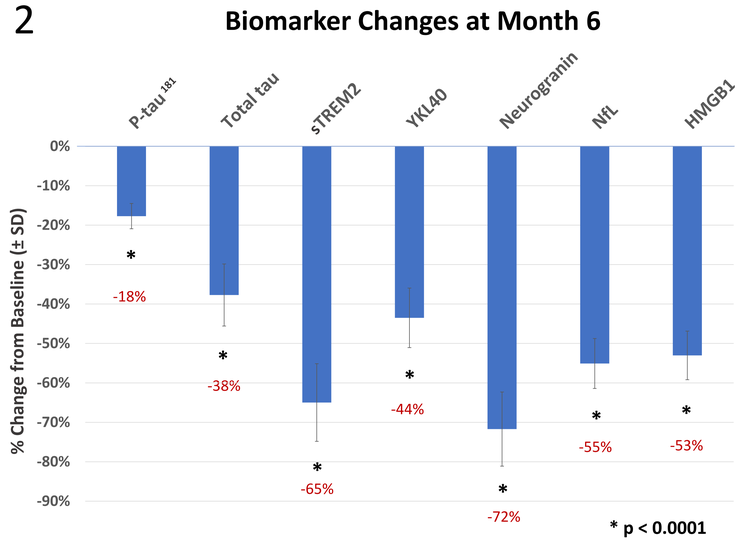
At baseline, 34% of these study subjects had no neuropsychiatric symptoms on the NPI. At 12 months, over 50% had no neuropsychiatric symptoms on the NPI.

Study Timepoint	No Neuropsychiatric Symptoms
Baseline	34% of subjects
6 months	38% of subjects
9 months	>50% of patients
12 months	>50% of patients

INTERIM RESULTS – CSF Biomarkers

Changes in CSF biomarkers were assessed in a subset of subjects (n=25) following 6 months of open-label simufilam treatment. CSF samples were analyzed in triplicate, blind to timepoint, by ELISA in an automated platereader. CSF P-tau[181], total tau, $A\beta_{42}$, sTREM2, YKL40, neurogranin, NfL, HMGB1 all showed profound improvements from baseline to Month 6 (Fig. 2; mean ± SD).

2



Not shown: $A\beta_{42}$ increased 84% from baseline to Month 6 (p<0.00001).

CONCLUSIONS

Simufilam 100 mg twice-daily continues to be safe and well-tolerated. CSF biomarkers from AD patients show profound improvements following six months of open-label treatment. In an AD patient population that is nominally expected to decline over time, ADAS-Cog11 scores improved in the first 50 study subjects to complete 6, 9 and 12 months of open-label treatment with simufilam, with 68% of subjects showing improved ADAS-Cog11 scores at Month 12. NPI also improved.

Simufilam's safety and efficacy is now being evaluated in a large, randomized-controlled Phase 3 clinical program across investigator sites in the U.S. and Canada under a Special Protocol Assessment (SPA) from the U.S. Food and Drug Administration (FDA).

REFERENCES

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