Simufilam

A novel small molecule in development for TSC-associated seizures

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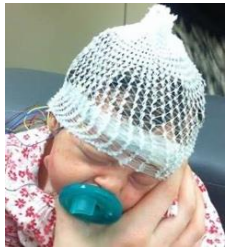
Simufilam:
A Novel Small Molecule in Development for TSC Associated Seizures

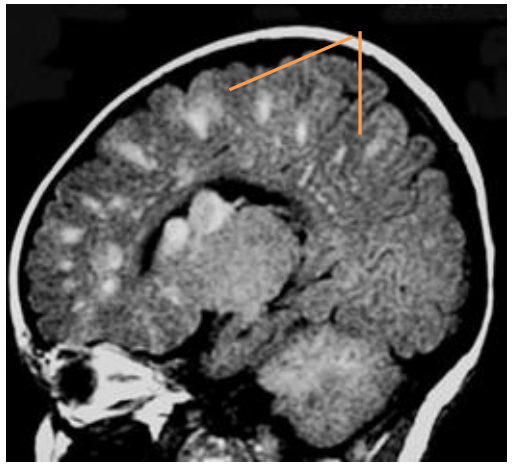
- Filamin A is an actin cross-linking protein that regulates critical cellular processes, including cell morphology, migration and differentiation
- Clinical and experimental evidence demonstrates alterations of filamin A expression in TSC and FCDII
- Simufilam has shown activity in animal models of TSC and FCDII
- The safety and tolerability profile of simufilam has been evaluated in a large clinical development program in Alzheimer's Disease
- Filana Therapeutics is planning a clinical development program for simufilam in TSC

Tuberous Sclerosis Complex

A genetic disorder characterized by seizures, neurologic impairments and multiorgan involvement



- Seizures in 85% of TSC patients
- Median age of seizure onset is 3 months

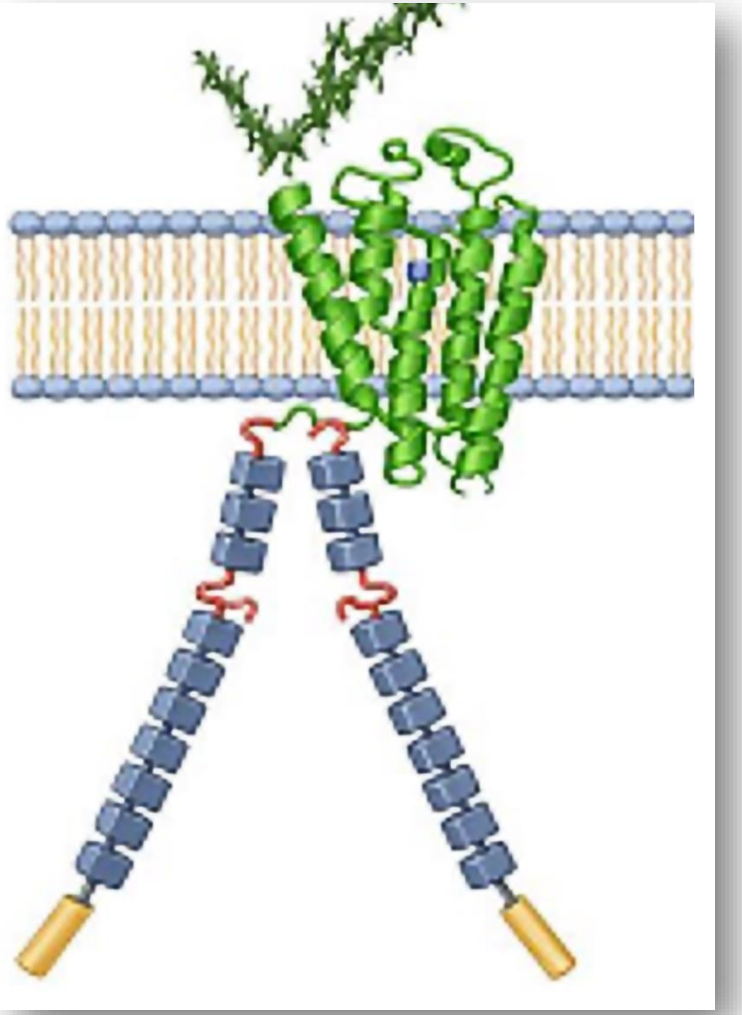


Characteristics	Standard of care	Comorbidities
• CNS tumors and other malformations • Skin lesions • Cardiac, renal and lung neoplasms • Behavioral and neurodevelopmental manifestations	• Antiseizure medications • Resective surgery • Neurostimulation • mTOR inhibitors • Supportive care	• Learning and cognitive impairments • Mood disorders • Autism • Sleep disturbances

TSC imposes a considerable burden on patients and their caregivers
There is a high unmet need for new approaches to treatment

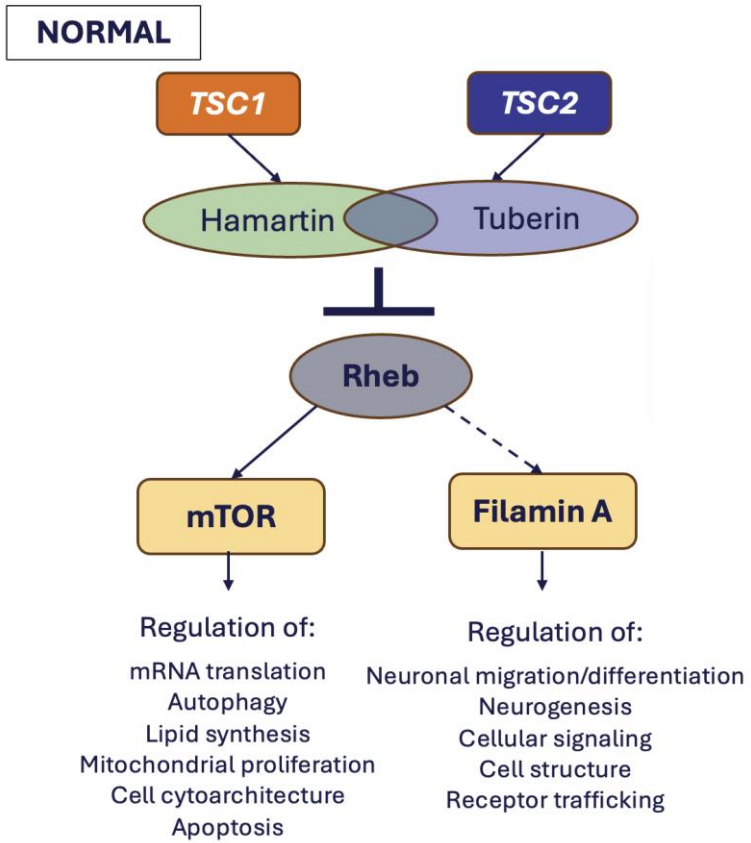
Filamin-A

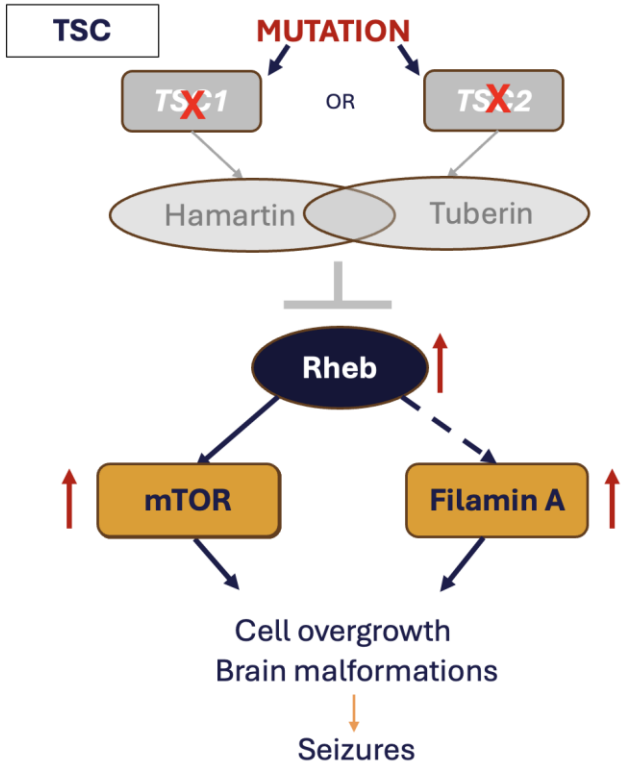
A potential target for treatment of TSC

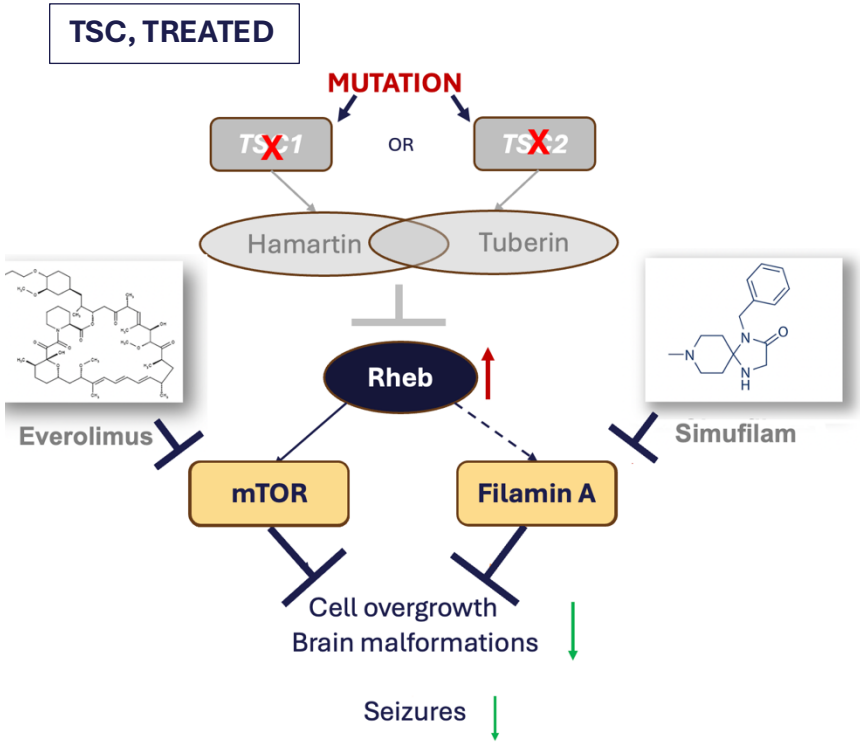


Filamin-A

- An actin cross-linking protein
- Present in muscle, connective tissue, vascular endothelium, brain and other tissues
- Abnormalities involving filamin A gene expression are implicated in
  - Tuberous sclerosis complex (TSC)
  - Focal cortical dysplasia type II (FCDII)







mTOR is a protein kinase that regulates numerous cellular metabolic processes. The ***TSC1*** and ***TSC2*** genes code for the proteins **hamartin** and **tuberin**, respectively. These form a heterodimer that **modulates the activity of mTOR via inactivation of the GTPase, Rheb.** Likewise, **filamin A expression is regulated via *TSC1/TSC2*–Rheb** via an mTOR-independent pathway.

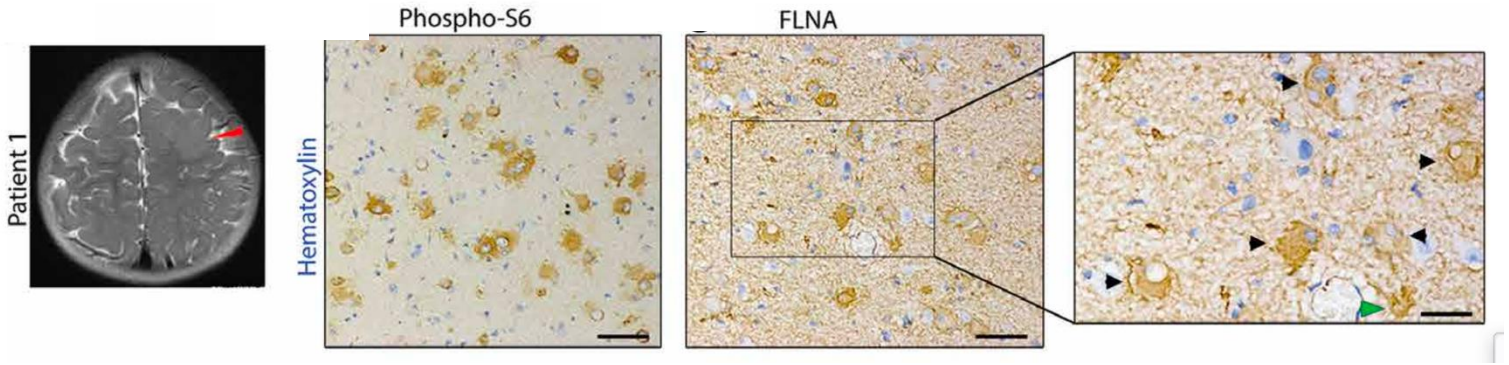
In TSC, **mutations in the *TSC1* or *TSC2* genes** disrupt formation of the hamartin-tuberin complex, resulting in **diminished regulation and overactivity of Rheb**. This, in turn, allows **hyperactivity of mTOR** and **altered filamin A expression**. In addition to the pathophysiologic contribution of mTOR, the increased expression of filamin A has been shown to contribute to brain malformations and seizures in a rat model of TSC.

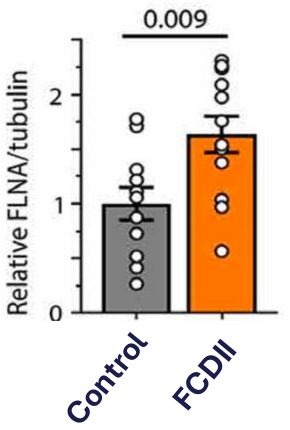
Everolimus is approved for the treatment of subependymal giant cell tumors and renal angiomyolipomas, as well as for adjunctive treatment of seizures, in TSC. **Simufilam is an investigational small molecule that modulates filamin A expression**, which has potential utility in the treatment of TSC-associated seizures. In mouse models of TSC and focal cortical dysplasia type II, it partially restores cellular architecture and reduces seizure activity.

Abbreviations: mTOR, mechanistic target of rapamycin; Rheb, RAS-homologue expressed in brain

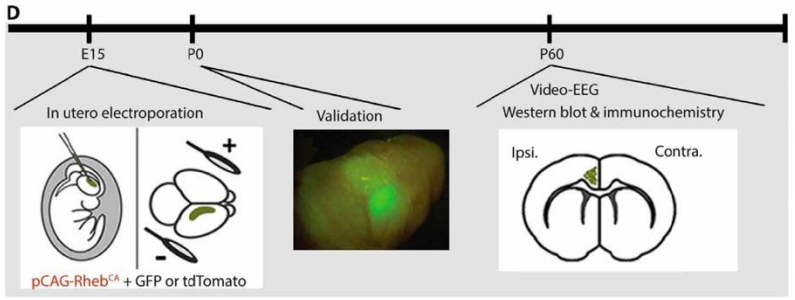
FLNA is elevated in clinical and experimental FCDII

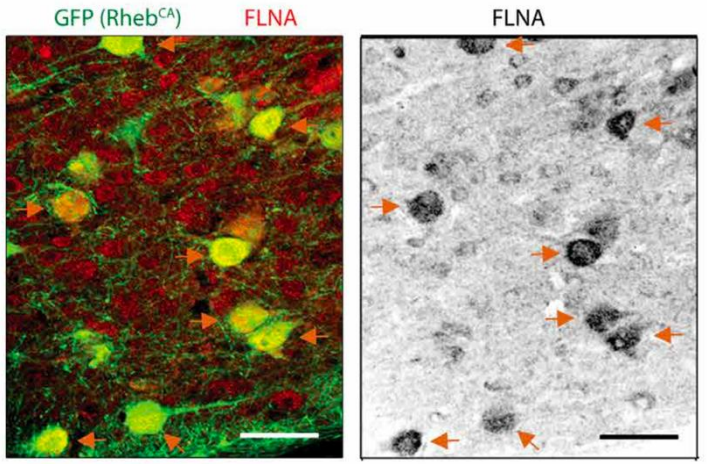
FCDII patient, resected cortical tissue

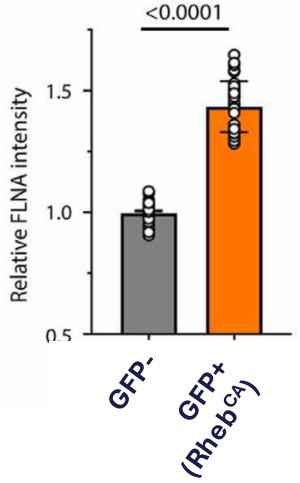




Rheb^{CA} expressing cells in FCDII mouse model



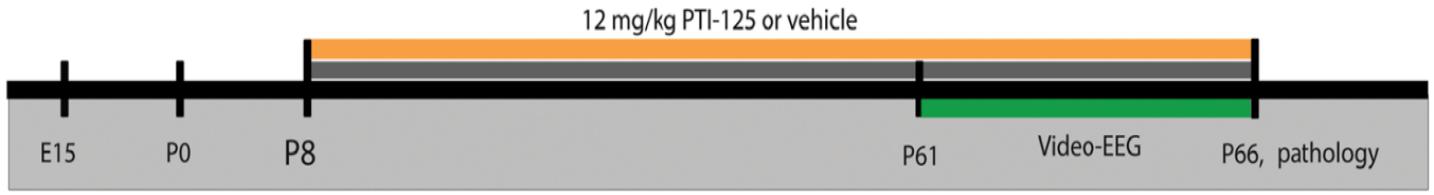


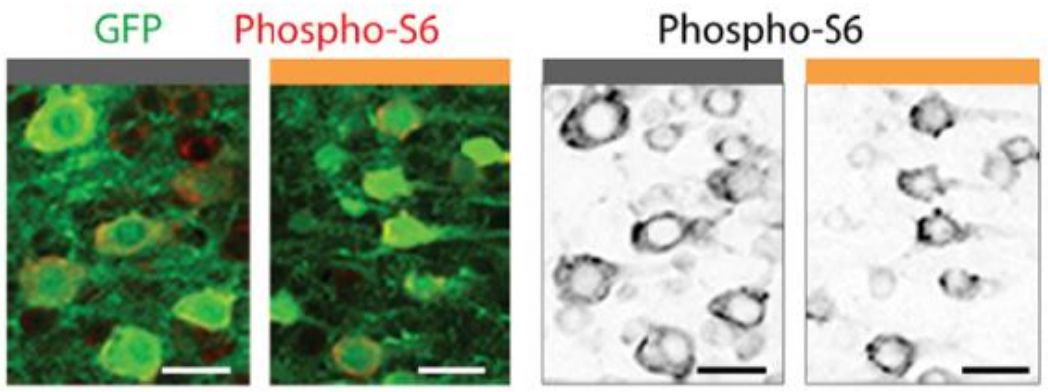


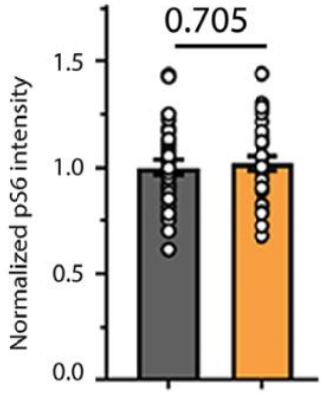
Zhang L, Huang T, Teaw S, et al. Science Translational Medicine 2020; 12:eaay0289.

Simufilam ameliorates cell structural derangements and seizures in a mouse model of FCDII

Experimental paradigm



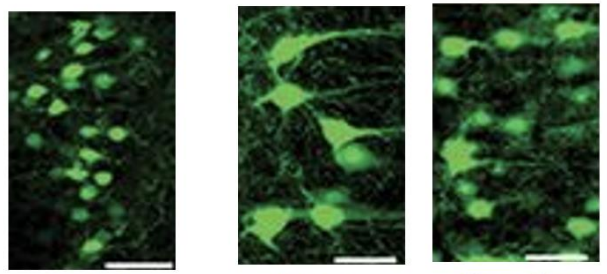




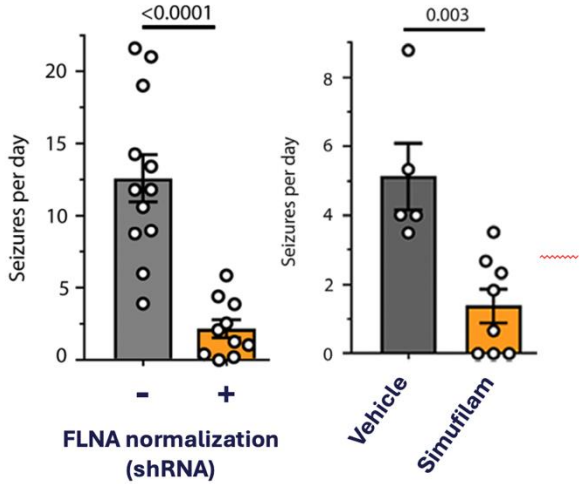
Normalizing the amount of FLNA in dysmorphic neurons of mTOR-driven focal cortical malformations partially prevents cytoarchitectural abnormalities

Simufilam treatment...

...reduces cell overgrowth



...recapitulates seizure reduction seen with FLNA normalization

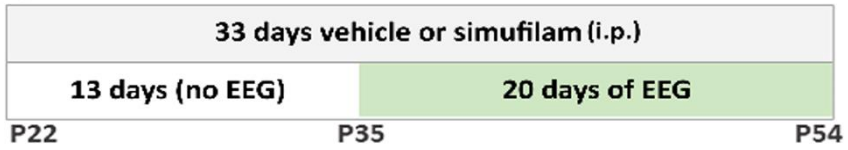


Zhang L, Huang T, Teaw S, et al. Science Translational Medicine 2020;12:eaay0289.

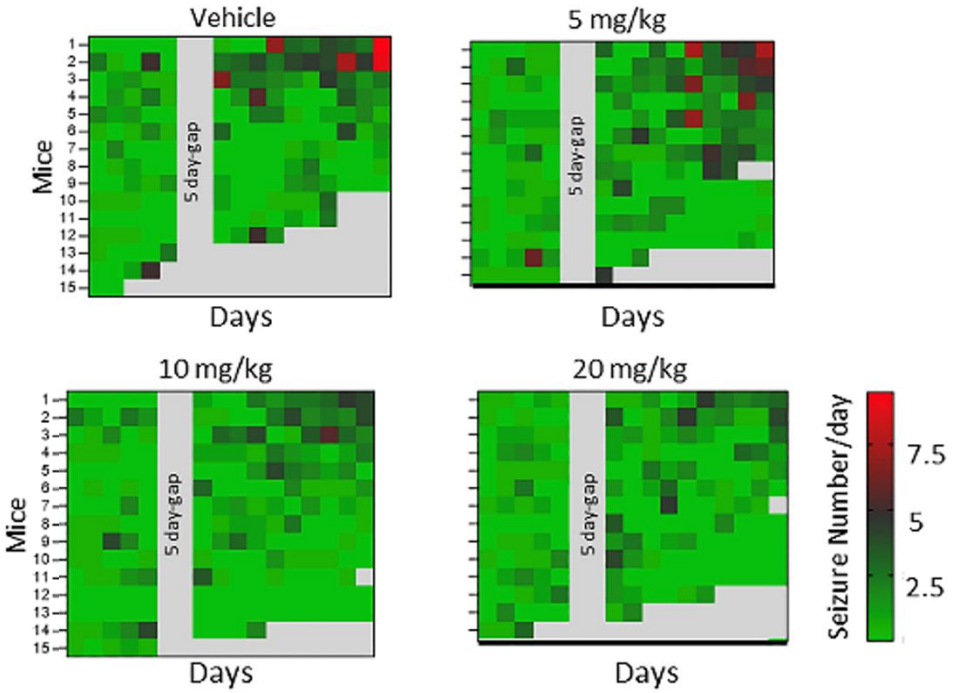
Simufilam prevented seizures in a Tsc1 conditional knockout mouse model

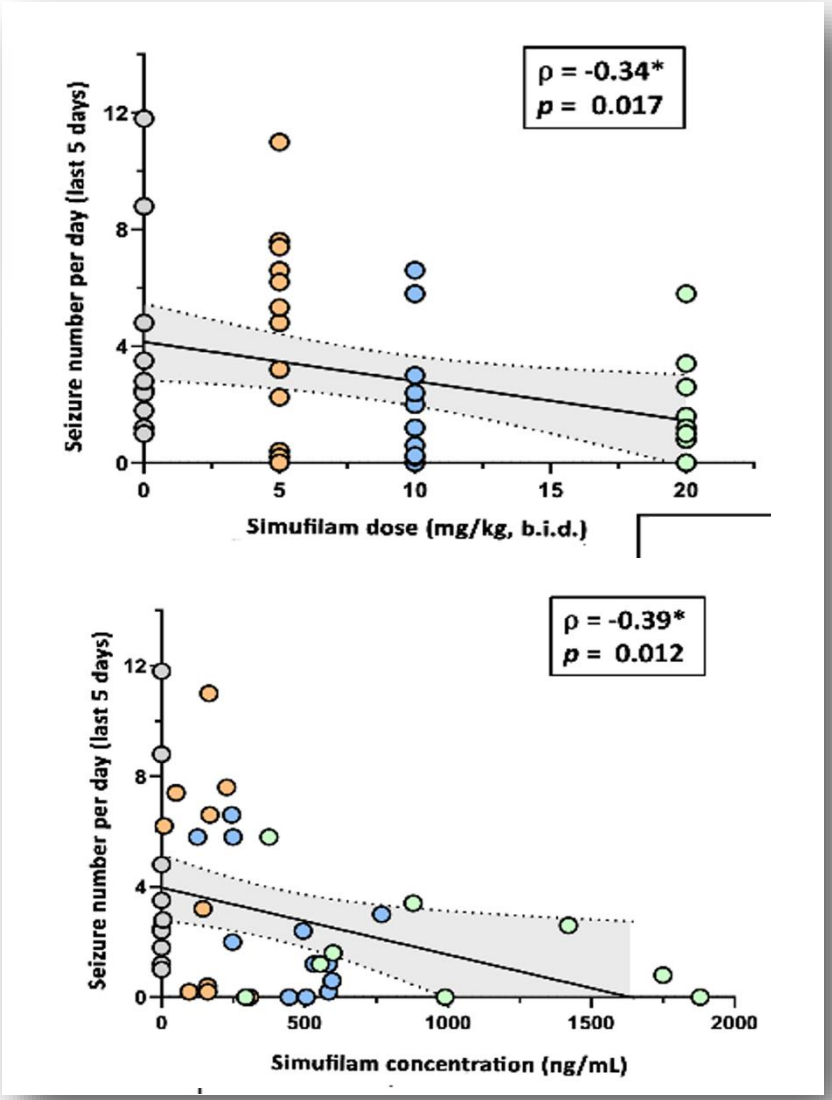
Effects were dose- and concentration dependent

Experimental paradigm

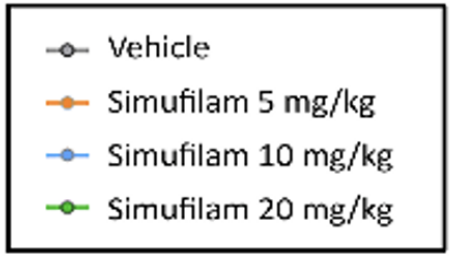


Heatmap of daily seizure number per mouse





Plot of the mean number of seizures per day on the last 5 days of monitoring (P50 – P54) as a function of simufilam doses (top) and plasma concentrations (bottom).



Stansley B, Islam MM, Aguiar DJ, et al. Epilepsia. 2026 Apr 14.

Simufilam safety and tolerability profile has been documented in over 1900 patients in two placebo-controlled trials in Alzheimer's Disease

- 1,409 patients reported at least one adverse event
- Low rate of individual adverse events
- Most were mild to moderate in severity
- Similar rates in active and placebo arms
- No serious adverse events assessed as related to study drug
- No evidence of emerging safety signals

Most frequent adverse events (≥3% simufilam)

Preferred Term	Simufilam 50 mg bid N = 376	Simufilam 100 mg bid N = 773	Placebo N = 771
COVID-19	49 (13.0%)	74 (9.6%)	76 (9.9%)
Fall	43 (11.4%)	62 (8.0%)	81 (10.5%)
Urinary Tract Infection	41 (10.9%)	63 (8.2%)	63 (8.2%)
Dizziness	11 (2.9%)	47 (6.1%)	24 (3.1%)
Diarrhea	19 (5.1%)	30 (3.9%)	31 (4.0%)
Headache	16 (4.3%)	35 (4.5%)	24 (3.1%)
Back Pain	16 (4.3%)	20 (2.6%)	16 (2.1%)
Agitation	16 (4.3%)	14 (1.8%)	19 (2.5%)
Anxiety	15 (4.0%)	27 (3.5%)	21 (2.7%)
Fatigue	15 (4.0%)	27 (3.5%)	21 (2.7%)
Arthralgia	14 (3.7%)	27 (3.5%)	29 (3.8%)
Depression	12 (3.2%)	19 (2.5%)	27 (3.5%)
Nausea	9 (2.4%)	23 (3.0%)	20 (2.6%)
Weight Decreased	6 (1.6%)	23 (3.0%)	18 (2.3%)
Constipation	6 (1.6%)	23 (3.0%)	19 (2.5%)

Pharmacokinetics and metabolism

Human SAD study

- Three cohorts of eight subjects each
- Six simufilam- and two placebo treated subjects per cohort

Parameter	50 mg Dose	100 mg Dose	200 mg Dose
T_{max} (h)	2.00 (0.67-2.00)	1.00 (0.68-2.00)	1.00 (0.67-2.00)
C_{max} (ng/mL)	315 (29.54)	550 (25.93)	1240 (21.76)
AUC_{last} (h*ng/mL)	2040 (41.13)	3130 (35.27)	8130 (18.56)
AUC_{inf} (h*ng/mL)	2050 (41.13)	3130 (35.24)	8130 (18.53)
AUC_{extrap} (%)	0.361 (45.5)	0.148 (24.20)	0.0710 (72.31)
$T_{1/2}$	6.05 (±3.87)	4.45 (±0.39)	5.93 (±3.87)

- Linear PK 50-200 mg
- Well tolerated
  - No serious AEs
  - 3 AEs in 2 subjects
  - No AEs considered related to drug

Metabolism

- Elimination via liver (36%) and kidney (64%)
- Major metabolizing enzyme - CYP2C19 (minor contribution from CYP2D6)
- Unchanged simufilam is major circulating entity; six metabolites detected; one major metabolite determined from pooled human plasma samples and phase 1 testing
- Do not anticipate clinical effects from coadministration of 2C19 inhibitors
  - Fractional metabolism – 36% from liver
  - Can evaluate estimated doses and concentrations using AD population
  - Favorable tolerability demonstrated in AD

Preliminary design: Phase 2 POC trial*

Study goals

- Safety and tolerability
- Pharmacokinetics in TSC population
- Inform dosing and other design aspects for Phase 3

KEY ENROLLMENT CRITERIA

Genetic or clinical diagnosis of TSC

Ages 12-50

8 seizures/mo.

1-5 concomitant ASMs

TREATMENT

Double-blind dose comparison

100 mg BID vs. 200 mg BID

4-week titration and 12-week maintenance

Open-label extension

ENDPOINTS

Percent reduction in countable seizures

CGI, CGI-seizure severity and duration

Sleep measures and nocturnal seizure frequency

*Pending outcome of regulatory discussions