ANAVEX®2-73 Increases Survival and Reduces Seizures in a Disease Model of Tuberous Sclerosis

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Background

The Sigma-1 receptor (σ1R) is dormant during normal conditions, but different types of stressors activate the receptor. σ1R activation results in numerous intracellular processes which restore cellular homoeostasis and neuroplasticity.

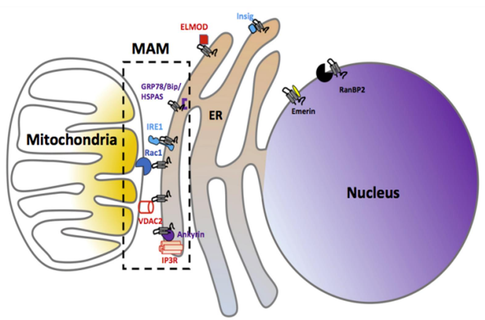
ANAVEX2-73 is a σ1R agonist that has demonstrated favorable safety, bioavailability, and tolerability in Phase 1/2 clinical trials. Data from the ongoing Phase 2a study in Alzheimer's disease patients demonstrate dose-dependent cognitive improvement. Given the reported ability of the σ1R to restore cellular homeostasis, neurodevelopmental disorders may also respond to the activation of σ1R in a disease-modifying manner. One such disorder is Tuberous Sclerosis (TSC) and the TSC1/2 mouse is a well-characterized model with a behavioral profile that mimics many aspects of the clinical picture.

Of particular interest was the impact of ANAVEX2-73 on seizure activity as this compound has previously been demonstrated to have a strong anti-epileptic effect in four different seizure models, including MES, PTZ, Infantile Spasms and Angelman Syndrome.

Prevalence of seizure activity in TSC is approximately 85% with 50% of those refractory to current anticonvulsant medications.

All experiments were conducted in the laboratories of PsychoGenics, Tarrytown, NY, in conjunction with the Tuberous Sclerosis Alliance.

Sigma-1 Receptor: Key Upstream Modulator that Restores Cellular Homeostasis



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The σ1R is an intracellular chaperone protein located at the endoplasmic reticulum–mitochondria interface with important roles in inter-organelle communication. σ1R is also involved in transcriptional regulation at the nuclear envelop and restores homeostasis and stimulates recovery of cell function when activated.

Methods

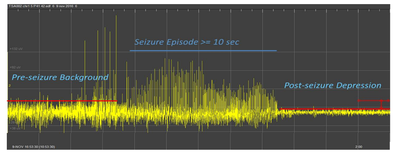
Tsc1^{GFAP}CKO mice were bred at PsychoGenics using breeding pairs obtained from Michael Wong's laboratory (Washington University, St. Louis, MO).

Prior to recording, *Tsc1*^{GFAP}CKO mice (Cre^{+}; *Tsc1*$^{flox/flox}$) were balanced among treatment groups.

EEG headmounts were implanted between Day (D) D23-P27 and continuously recorded from D35-P53.

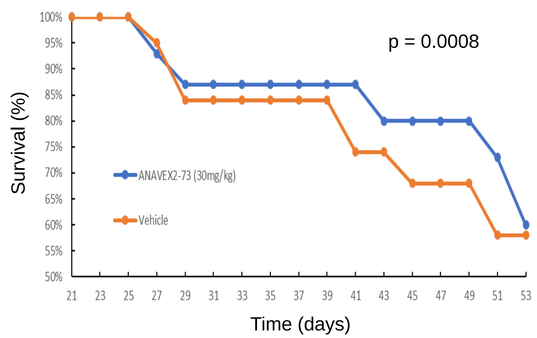
Once daily dosing with test compounds began on Treatment Day ~D21 and continued until ~D53: ANAVEX2-73 (30 mg/kg/day PO), vehicle (tween 80, 5% PEG, 4% ethanol in 0.9% saline), positive control (rapamycin; 3 mg/kg/day IP).

EEG recordings were analyzed during week 5 and 6 for number of seizures as described previously (Zhang et al., 2013).



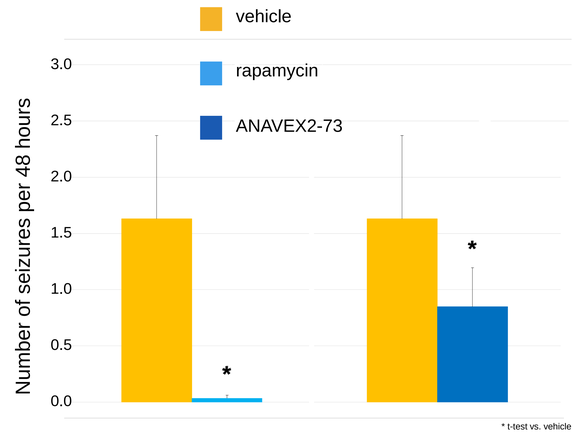
Screen capture from an EEG recording from parietal cortex of a Tsc1 mouse showing a single seizure episode. Inset labels define criteria used to identify individual seizures.

ANAVEX2-73 Significantly Increases Survival of Tsc1 CKO Mice



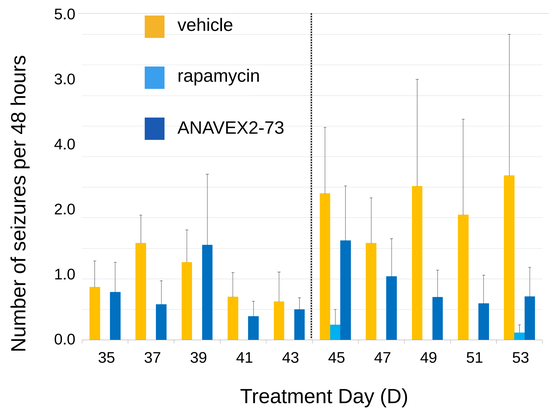
- *Tsc1* CKO mice treated with ANAVEX2-73 (30 mg/kg/day PO) showed a significant improvement in survival compared to vehicle-treated control animals (p = 0.0008).
- In these experiments, rapamycin (3 mg/kg/day IP) served as the positive control, thus validating the results with the test compound (data not shown).

ANAVEX2-73 Significantly Reduces the Seizures in Tsc1 CKO Mice



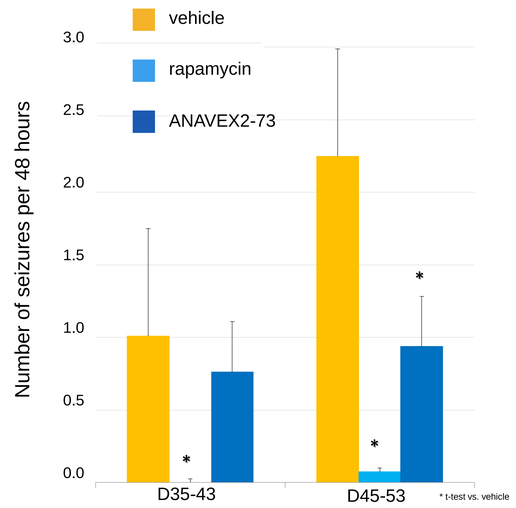
- *Tsc1* CKO mice treated with ANAVEX2-73 (30 mg/kg/day PO) showed a significant reduction in seizures recorded over 48 hours (p < 0.05 vs. vehicle-treated mice).
- In these experiments, rapamycin (3 mg/kg/day IP) served as the positive control, thus validating the results with the test compound.

Seizures in the Vehicle Group Increase with Age, Which is Prevented with ANAVEX2-73



- Seizures in *Tsc1* CKO mice in the vehicle group increase with age, however, treatment with ANAVEX2-73 (30 mg/kg/day PO) prevented this increase.

Summary of Age-Related Changes in Seizure Frequency



- Summary graph illustrating the age-dependence of the effect of ANAVEX2-73 (30 mg/kg/day PO) in reducing seizure frequency.

Summary

Overall, these findings demonstrate that treating TSC1/2 mice with ANAVEX2-73 significantly reduces seizure activity, and increases survival.

The anti-epileptic effect of ANAVEX2-73 in this TSC model is consistent with the compound's effect in four other animal seizure models, including the orphan diseases Infantile Spasms and Angelman Syndrome.

The results obtained in previous disease models, including both chemical and genetic manipulations, suggest that targeting σ1R might be of significant benefit regardless of the underlying pathology.

Conclusions

Collectively, these results suggest a role for ANAVEX2-73 as a potential treatment for a wide range of diseases, including rare neurodevelopmental diseases, that elicit seizures.