W105

TRV045, a novel, selective $S1P_1$ receptor modulator that is not an immunosuppressant, is efficacious in rodent models of epilepsy

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BACKGROUND

S1P subtype 1 receptors are highly expressed in the CNS and are important in brain development and perpetuation of brain inflammation, as well as in the formation and preservation of the blood brain barrier. Because of their functions and localization in the brain, $S1P_1$ receptors should be investigated as a potential target for the prevention/ treatment of epilepsy.

Fingolimod (GILENYA®), a non-selective S1P receptor modulator, exerts significant antiepileptogenic effects in rodent models (1-4). Because fingolimod is not selective, it has not been established which subtype is responsible for the beneficial effects demonstrated in these models. Importantly, while fingolimod has provided evidence that targeting S1P receptors could have potential benefits for the treatment of epilepsy, fingolimod is an immunosuppressor, which can greatly limit the use of this molecule for epilepsy.

Trevena has synthesized a class of molecules that potently and selectively activate $S1P_1$ receptors and that are not immunosuppressant in mice and non-human primates. In collaboration with the NINDS Epilepsy Therapy Screening Program (ETSP) we have initiated the screening of TRV045 as a potential anti-epileptic treatment in a battery of well-established rodent seizure models.

OBJECTIVES

Investigate the efficacy of a selective, non-immunosuppressant $S1P_1$ receptor modulator in rodent epilepsy models in acute and protective mode.

METHODS

In the **maximal electroshock seizure (MES)** model, 60Hz of alternating current (150 mA) was delivered in rats for 0.2 sec by corneal electrodes. Sprague Dawley rats (n=8) were initially tested for seizure activity 0.25, 0.5, 1, and 2 hr following s.c. injections of vehicle only [10% DMAC/ 10% cremophor/ 0.1% TWEEN 80/ 79.9% (10% HPβCD in sterile water)] or TRV045 to determine time of peak effect (TPE). An animal was considered "protected" from convulsant activity upon abolition of the hindlimb tonic extensor component of the seizure. An ED50 dose was then determined by dosing rats s.c. (n=8/group) and testing at the TPE (1 hr).

In the **Theiler's murine encephalitis virus** model (TMEV), C57Bl6/J mice were pretreated with TRV045 for 2 days (10mg/kg, BID, s.c.) prior to TMEV inoculation. Two hours following dosing on the 3rd day, animals were infected with TMEV. Mice were then treated with TRV045 and monitored for seizure activity twice per day for another 7 days.

In the **corneal kindled seizure model**, C57Bl/6 mice were kindled electrically with corneal electrodes to a criterion of 5 consecutive stage 5 seizures (5). Fully kindled mice were then stimulated every other day until all mice within each group reached the criterion of 5 consecutive stage 5 seizures. Testing of TRV045 commenced 5-7 days after the last stimulation. TRV045 was initially dosed at 10 mg/kg s.c. (n=8/group) and mice were tested at 1 and 2 hr after dosing to determine TPE. An ED50 dose was then determined by dosing mice subcutaneously (n=8/group) and testing at the TPE (2 hr).

In the **chronic model of mesial temporal lobe epilepsy (mTLE)**, C57Bl/6 mice were treated with a unilateral intrahippocampal infusion of kainic acid (KA) to induce spontaneous hippocampal paroxysmal discharges (HPDs) 2-3 weeks post-infusion. After KA injection, all mice were implanted with a bipolar electrode into the injected hippocampus and a reference electrode over the cerebellum. The electroencephalogram (EEG) was recorded in freely moving animals. A total of 7 mice were evaluated for treatment effect (TRV045, 6 mg/kg, s.c.) at 2 hours post-drug administration, with the mean baseline HPD count determined prior to drug administration. These studies were conducted by SynapCell, Inc. (France).

RESULTS

TRV045 efficacy in rat MES test.
20 mg/kg TRV045 was administered subcutaneously

Time after administration of TRV045 (hr)	0.25	0.5	1	2
Number of rats protected/total number of rats tested	1/8	3/8	4/8	0/8
Number of rats showing AEs/total number of rats tested	0/4	0/4	0/4	0/4

Figure 1. TRV045 dose-dependently protect rat from seizures in the rat MES model

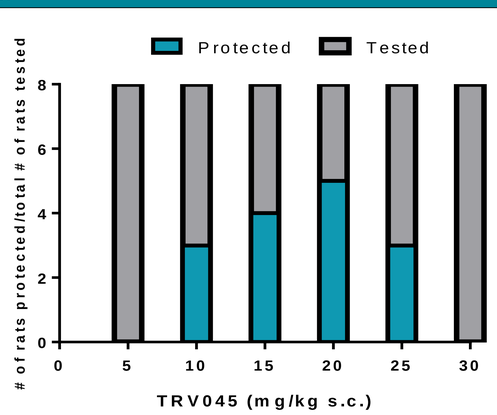


Figure 2. TRV045 at 10 mg/kg s.c. shows a trend in decreasing seizure burden in TMEV-treated mice

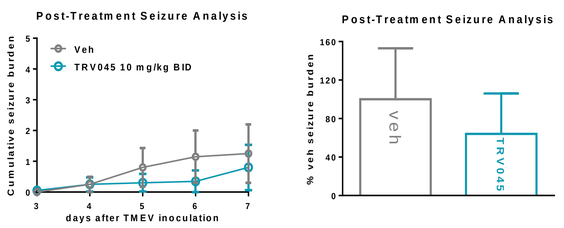
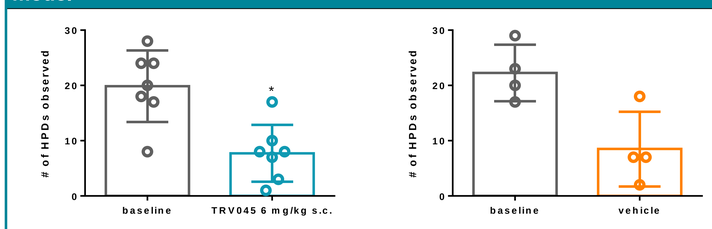
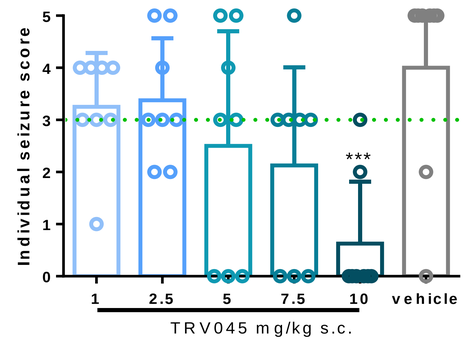


Figure 3. Vehicle-effect prevented assessment of TRV045-effect in mTLE model



Statistical analysis: * P<0.05; TRV045 vs baseline (paired t-test)

Figure 4. TRV045 dose-response in the mouse corneal kindled model. The calculated ED50 is 6.2 mg/kg s.c.



Statistical analysis: *** P<0.01, vehicle vs. treatment groups, one-way ANOVA followed by Dunnett's test

CONCLUSIONS

TRV045 is a selective $S1P_1$ receptor modulator that is currently being tested as protective agent in rodent models of epilepsy.

The scientific rational for initiating these studies is the previously published results with fingolimod. The efficacy of fingolimod in rodent models of epilepsy has provided positive evidence that targeting S1P receptors could have potential benefits.

In a poster presented at this meeting (T125) we have demonstrated that TRV045, unlike currently available S1P receptor modulators, does not cause lymphopenia and therefore is suitable for investigation in a variety of indications, including epilepsy.

The interpretation of the TRV045 epilepsy data presented here are confounded in some of the models by an apparent anti-epileptic effect of the vehicle. For instance, in the mTLE assay a decreased number of spontaneous hippocampal paroxysmal discharges is observed in a group of mice administered with vehicle only. Further characterization of this confounding effect with a different vehicle preparation will be needed to clarify this observation.

In summary, these preliminary data suggest that selective modulation of $S1P_1$ receptors by TRV045 could be a therapeutic target for epilepsy. This novel mechanism of action may provide a new therapeutic option for the treatment of epilepsy.

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Disclosure

TRV045 is an investigational drug developed by Trevena, Inc.

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