Figure 1 (a)

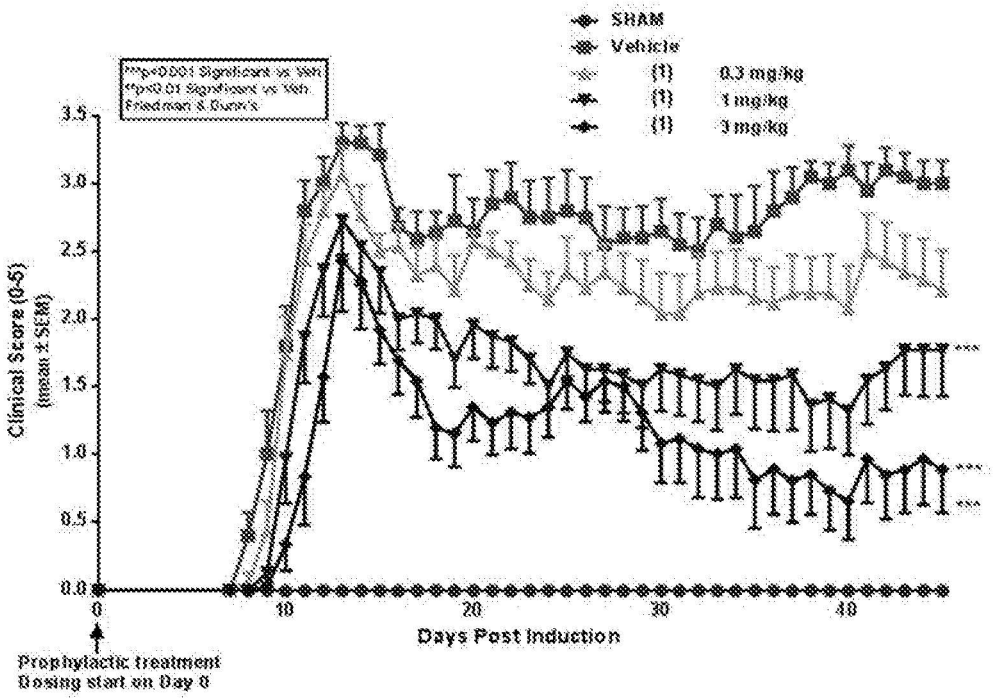


Figure 1 (b)

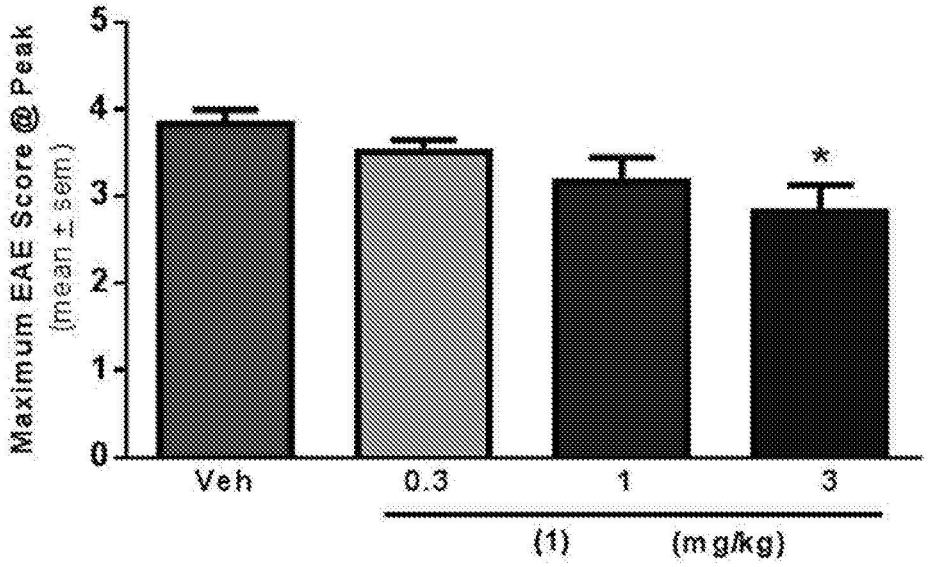


Figure 1 (c)

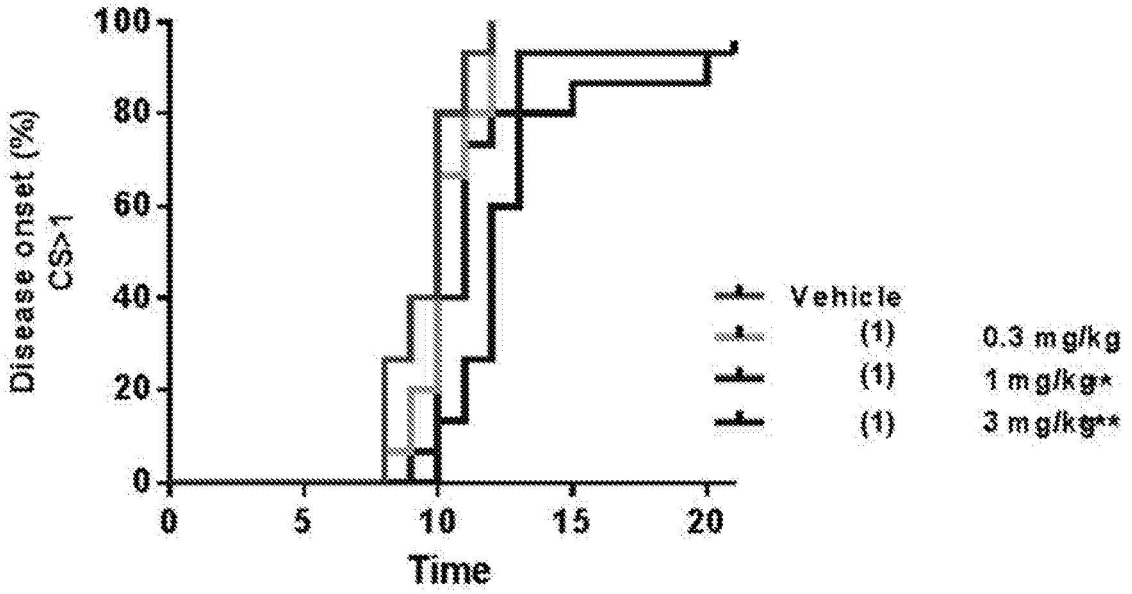


Figure 1 (d)

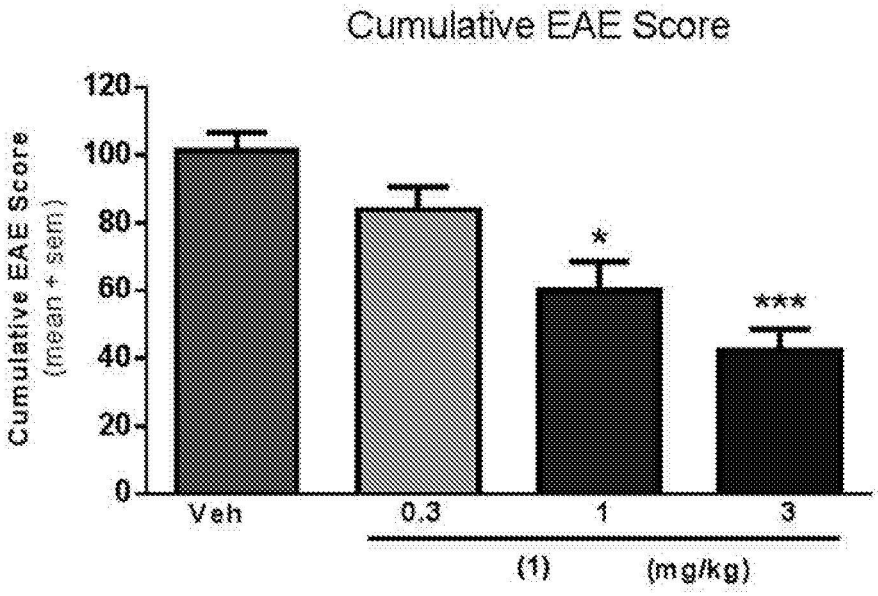


Figure 2 (a)

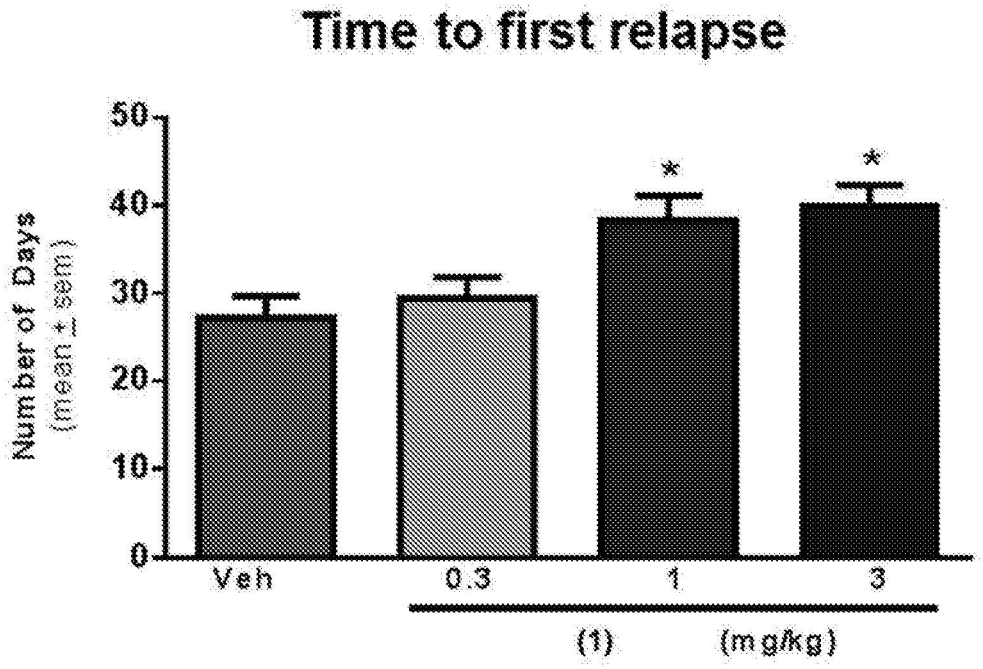


Figure 2 (b)

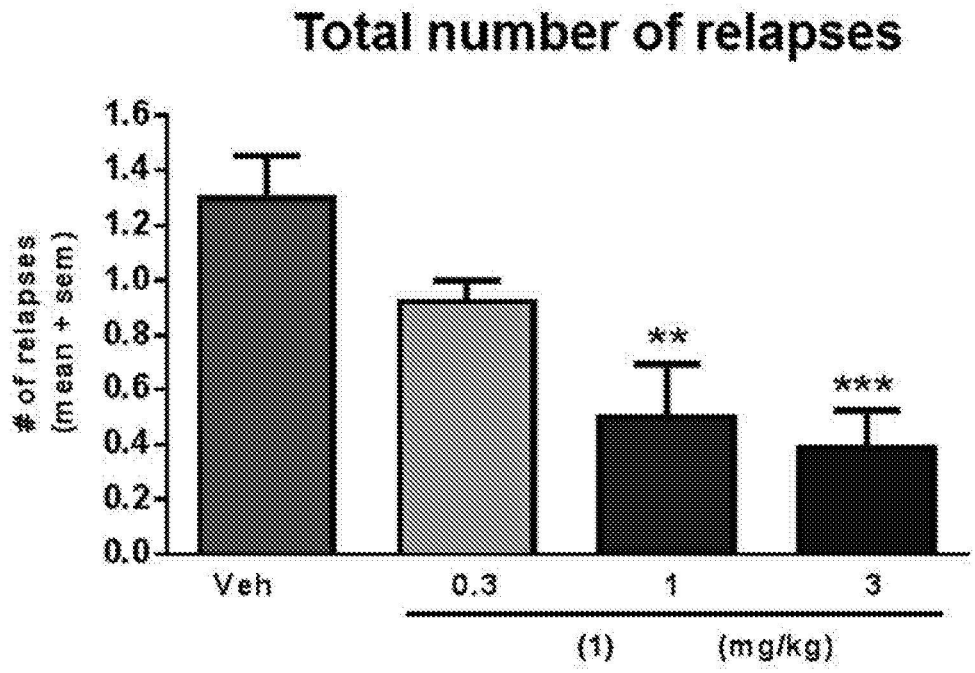


Figure 2 (c)

	Incidence (%)	Relapse (%)
Vehicle	100	100
(1) 0.3 mg/kg	100	92
(1) 1 mg/kg	93	42
(1) 3 mg/kg	93	38

Figure 3 (a)

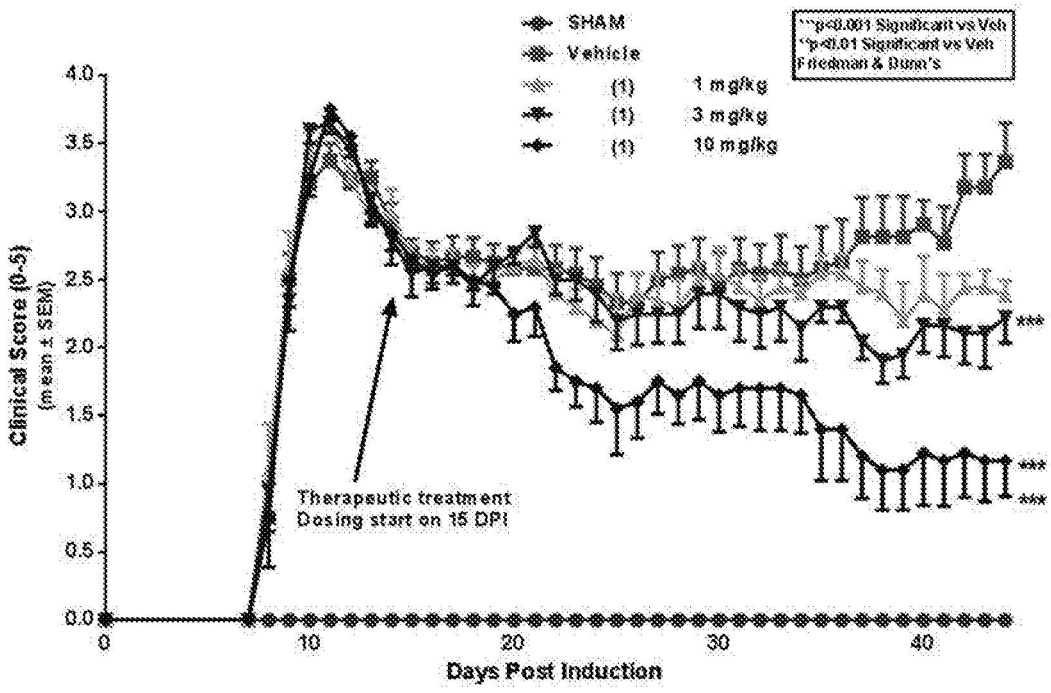


Figure 3 (b)

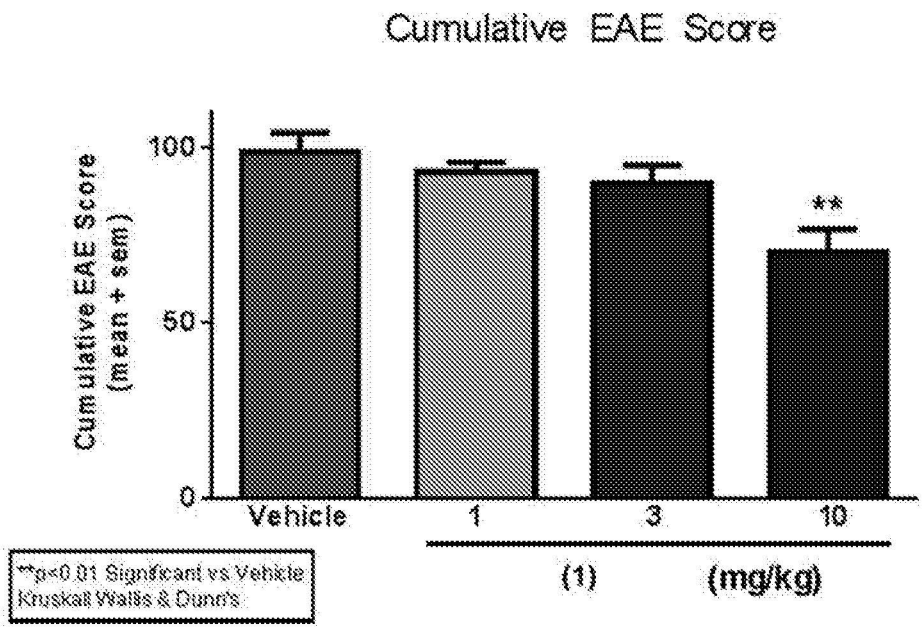


Figure 4 (a)

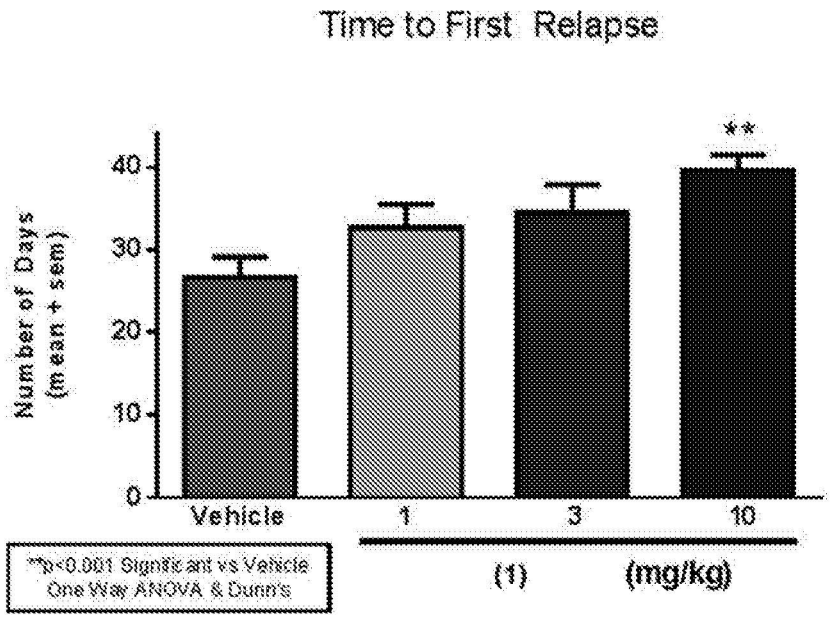


Figure 4 (b)

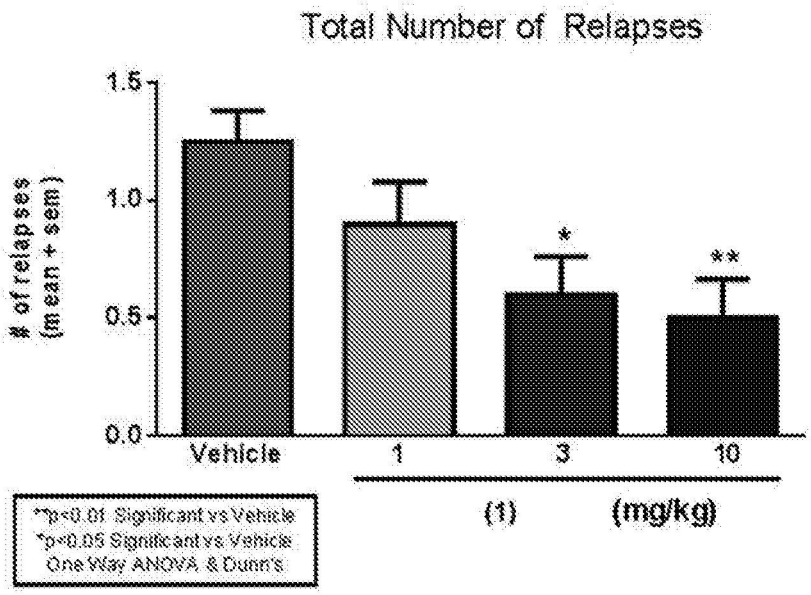


Figure 4 (c)

	Relapse (%)
Vehicle	100
(1) 1 mg/kg	80
(1) 3 mg/kg	60
(1) 10 mg/kg	50

Figure 5

treatment regimen	Dose (mg/kg)	Incidence (%)	Relapse (%)	Time to relapse (mean; days)	# of relapses (mean)	Cumulative EAE score (mean)
Prophylactic	Veh	100	100	27	1.3	101
	0.3	100	92	30	0.9	84
	1	93	42	38 *	0.5 **	60 *
	3	93	38	39 *	0.4 ***	42 ***
Therapeutic	Veh	n/a	100	27	1.25	97
	1	n/a	80	33	0.9	93
	3	n/a	60	34	0.6 *	90
	10	n/a	50	40 **	0.5 **	70 **

Figure 6 (a)

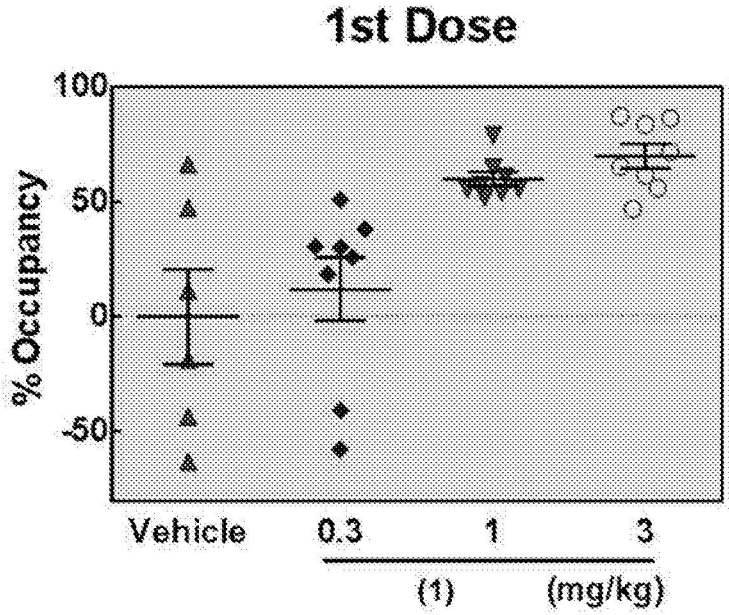


Figure 6 (b)

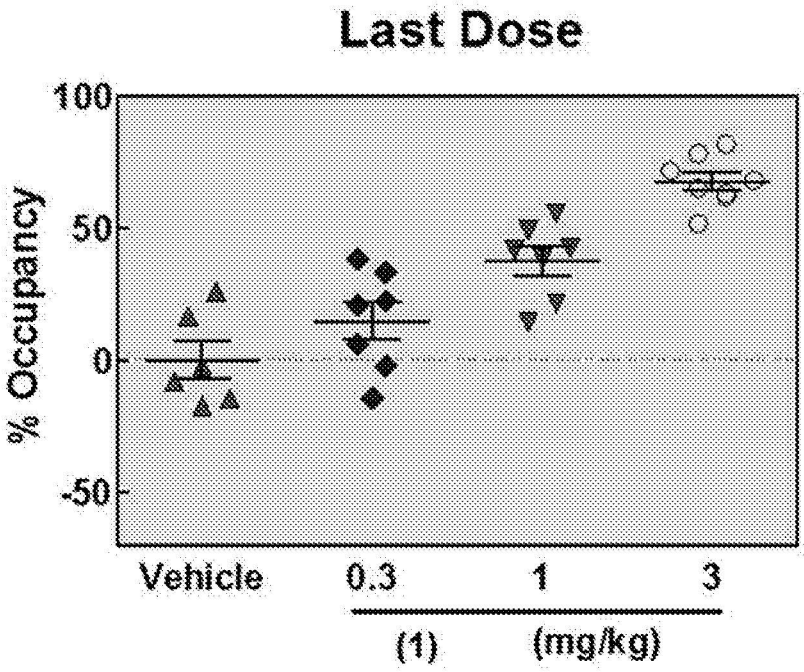


Figure 7 (a)

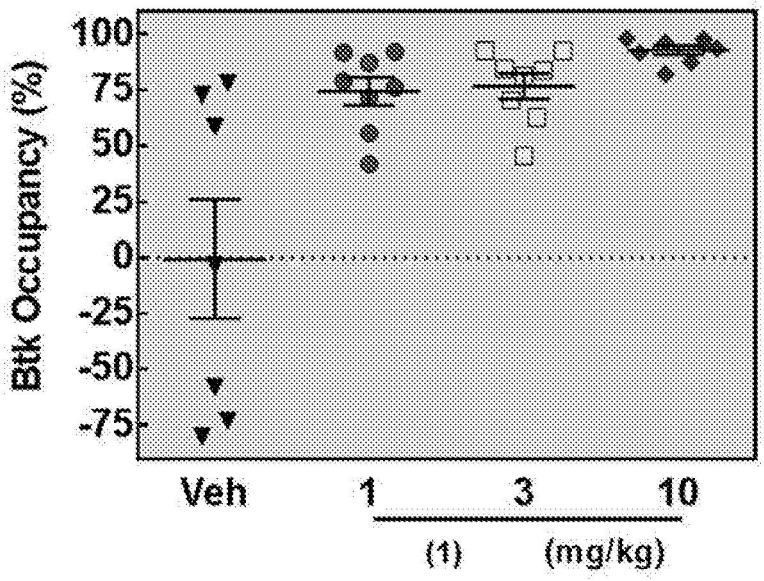


Figure 7 (b)

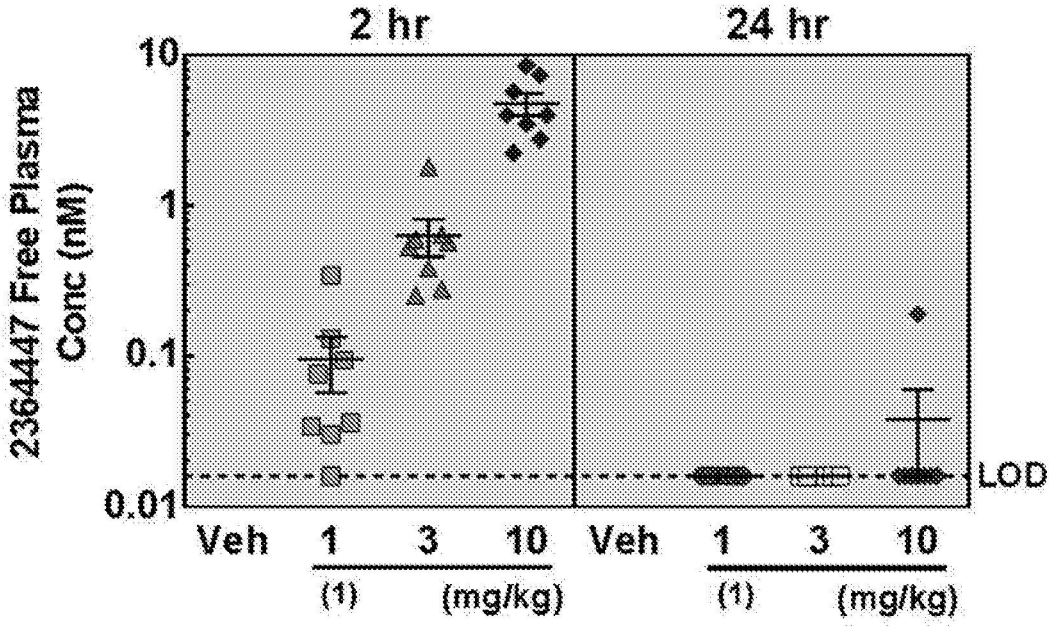


Figure 8

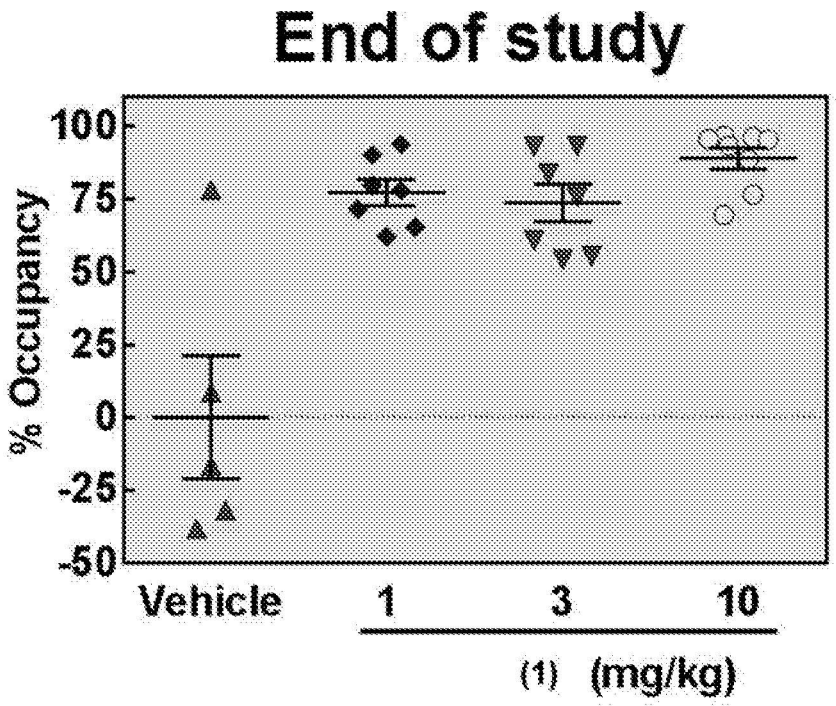


Figure 9 (a)

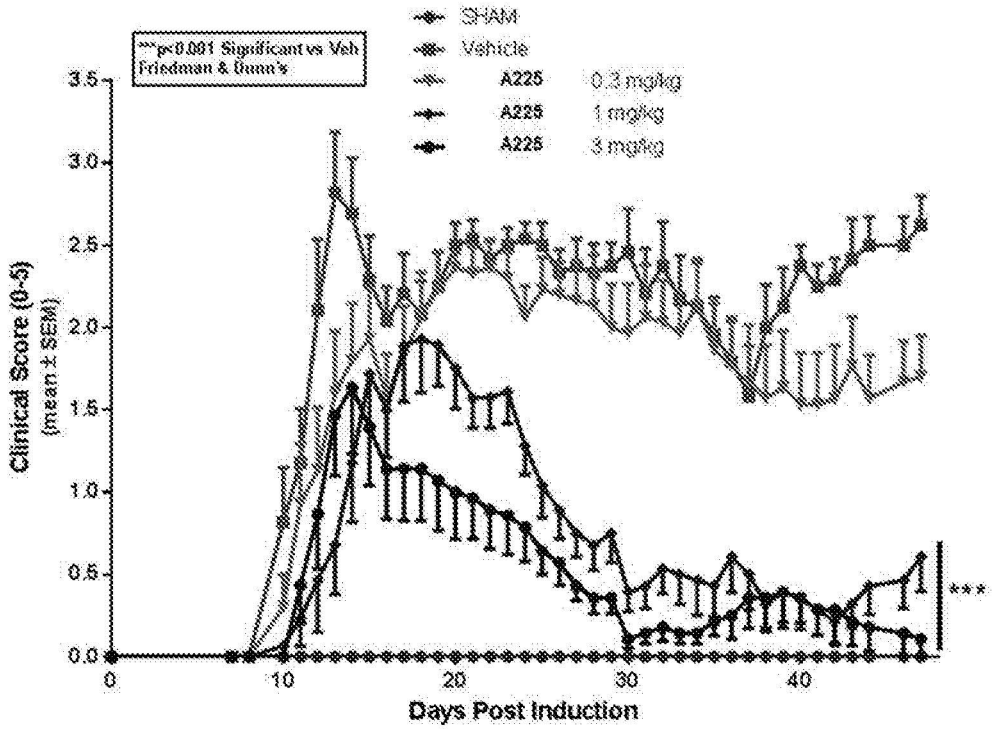


Figure 9 (b)

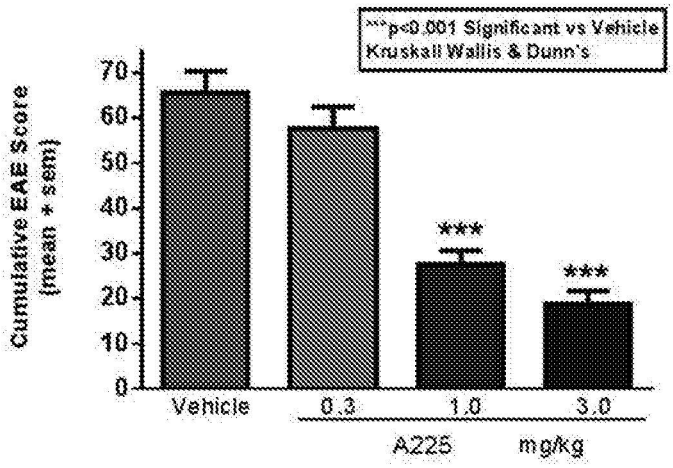


Figure 10 (a)

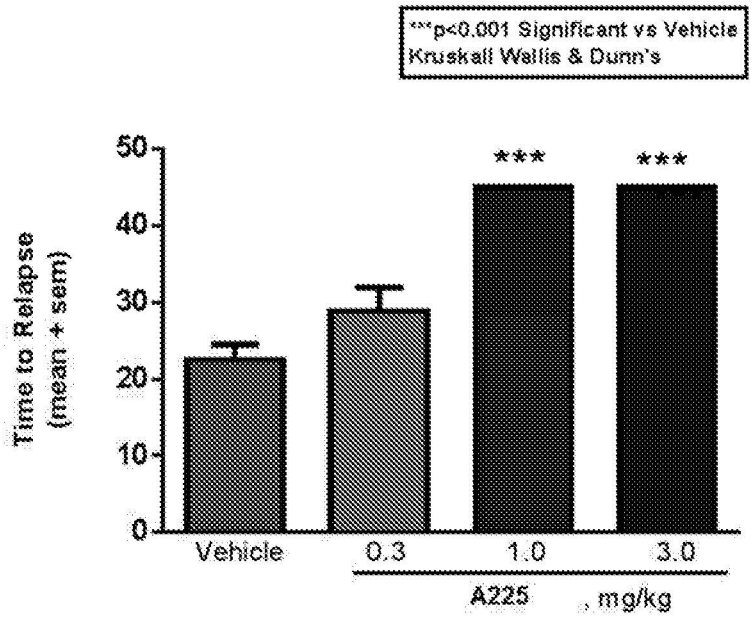


Figure 10 (b)

	EAE INCIDENCE (%)	RELAPSE (%)
Vehicle	**100**	**100**
(A225) 0.3 mg/kg	**93**	**73**
(A225) 1 mg/kg	**87**	**0**
(A225) 3 mg/kg	**53**	**0**

Figure 11

1. Dose mice in the PLP model of EAE with Btk inhibitors
2. On Day 42 after the start of PLP and treatment give mice oral dose of compound.
3. Collect blood 2 hr and 24 hr after dosing (NDD)
4. Lyse RBCs and perform WBC treatment with biotinylated probe (ATB). Use 15 ul of blood for dried blood spot PK analysis (ATB). Analyze for CD69 upregulation (Yin Wu).
5. Lyse cells and perform streptavidin capture MSD Btk occupancy assay (ATB)
6. Measure plasma compound concentrations using dried blood spot analysis and low detection limit format (Hui Tian, Yi-Ying Chen)

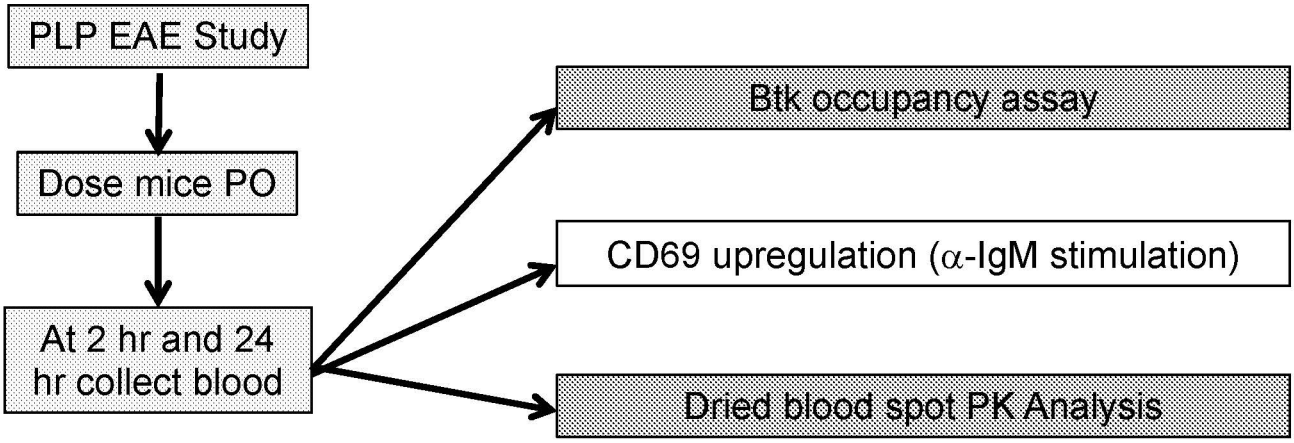


Figure 12 (a)

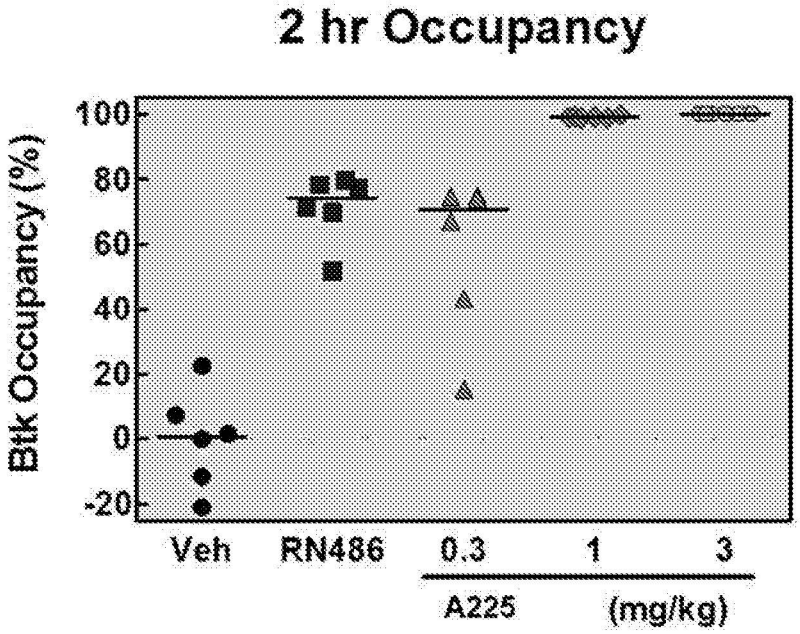


Figure 12 (b)

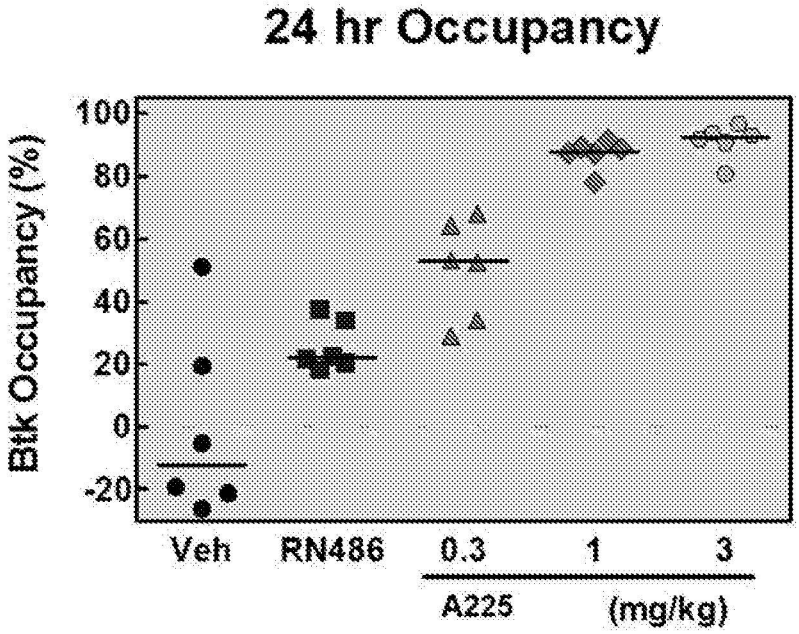


Figure 13

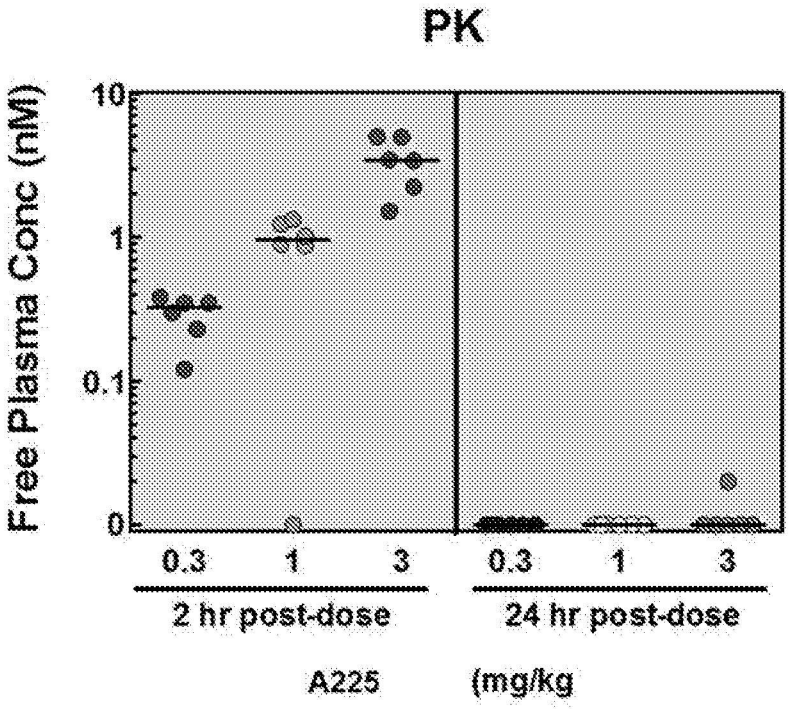

PK
Free Plasma Conc (nM)
10
1
0.1
0
0.3
1
3
0.3
1
3
2 hr post-dose
24 hr post-dose
A225
(mg/kg

Figure 14 (a)

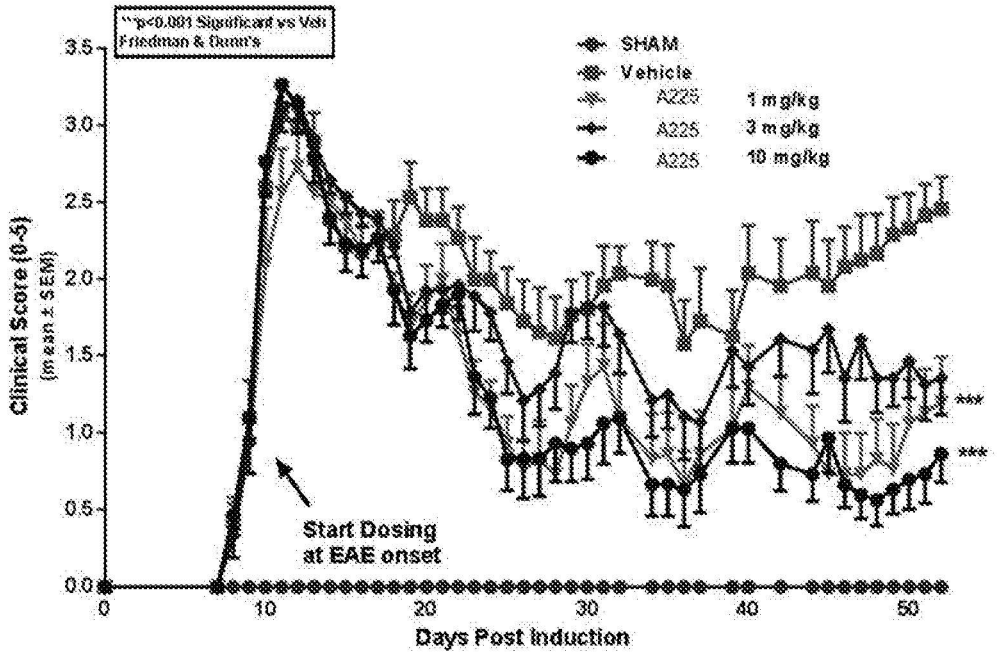


Figure 14 (b)

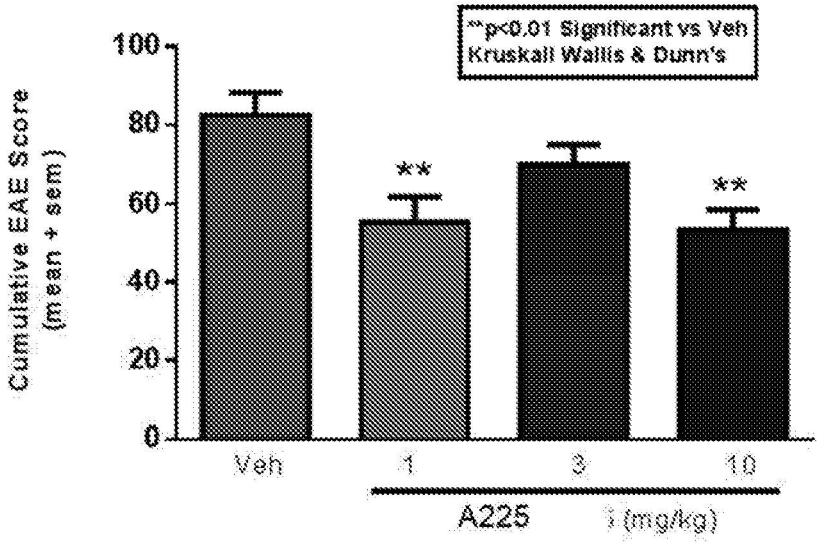


Figure 15 (a)

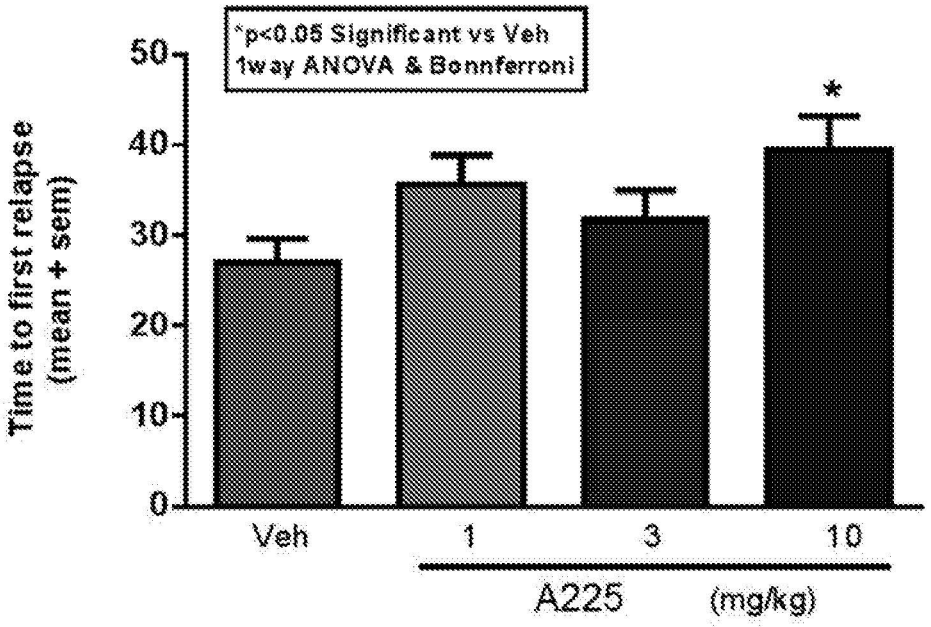


Figure 15 (b)

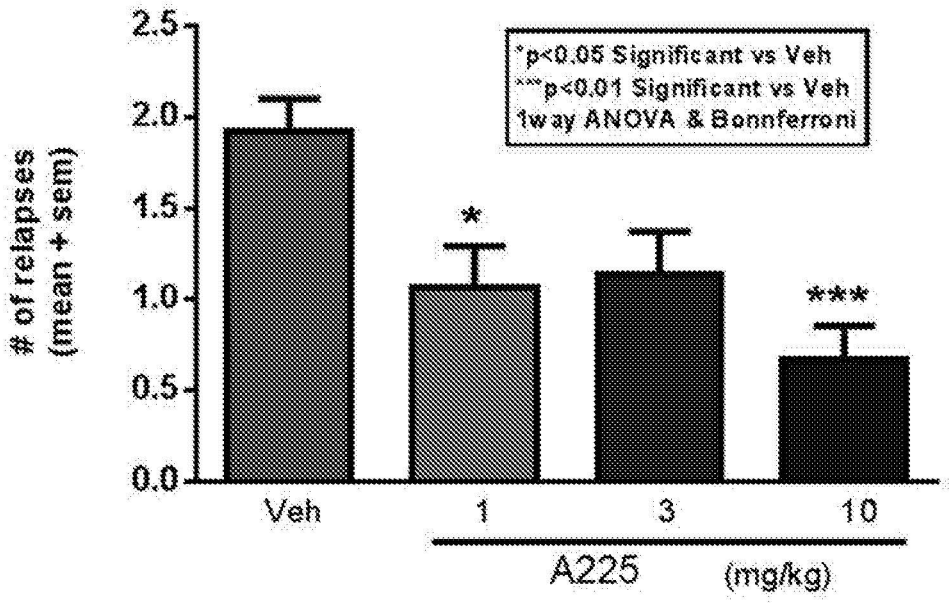


Figure 15 (c)

	RELAPSE BY END OF STUDY (%)
Vehicle	100
(A225) 1 mg/kg	73
(A225) 3 mg/kg	80
(A225) 10 mg/kg	60

Figure 16

1. On day 10 after PLP treatment start to dose SJL mice in the PLP model of EAE with Btk inhibitors
2. On Day 43 after PLP treatment, administer mice an oral dose of compound (RN486 30 mg/kg, A225 dose response).
3. Collect blood 2 hr and 24 hr after dosing (NDD TC)
4. Lyse RBCs and perform WBC treatment with biotinylated probe (ATB). Use 15 ul of blood for dried blood spot PK analysis (ATB). Analyze for CD69 upregulation (ES).
5. Lyse cells and perform streptavidin capture MSD Btk occupancy assay (ATB)
6. Measure plasma compound concentrations using dried blood spot analysis and low detection limit format (HT, YC)

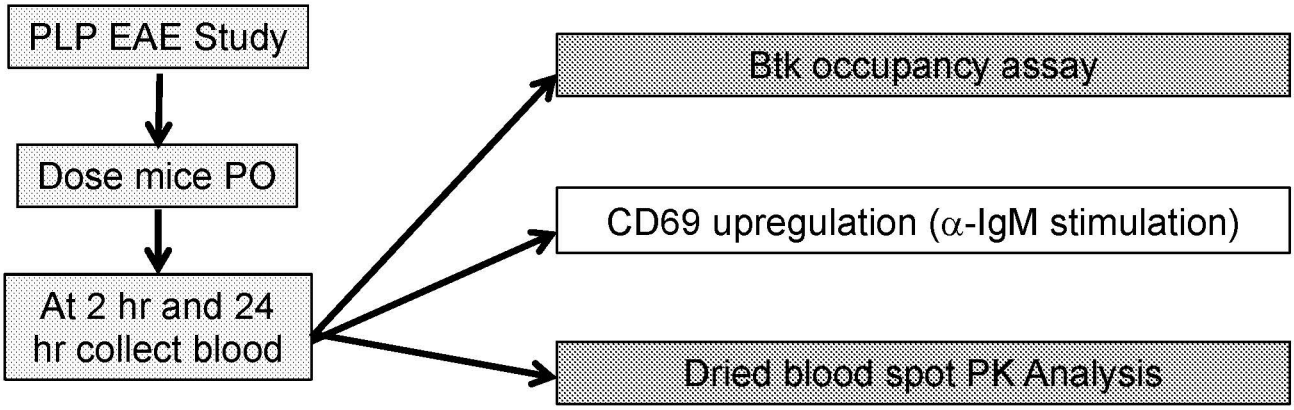


Figure 17 (a)

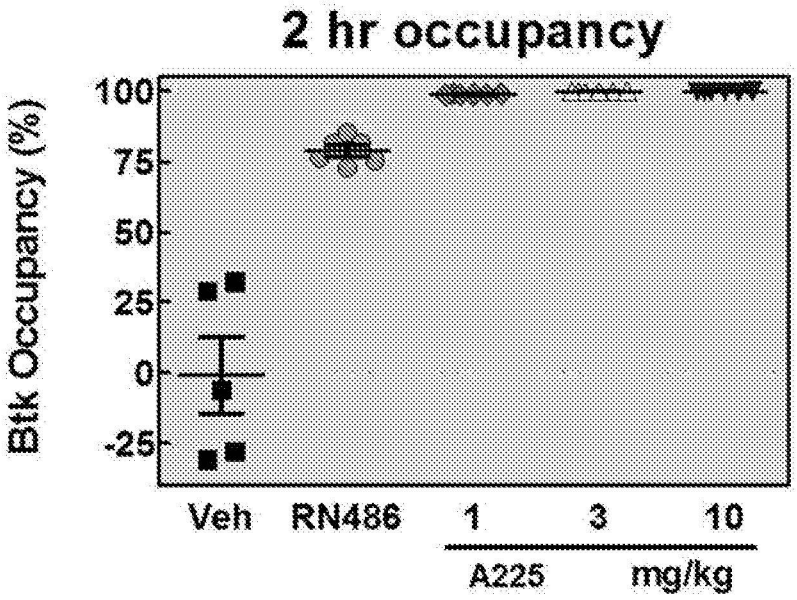


Figure 17 (b)

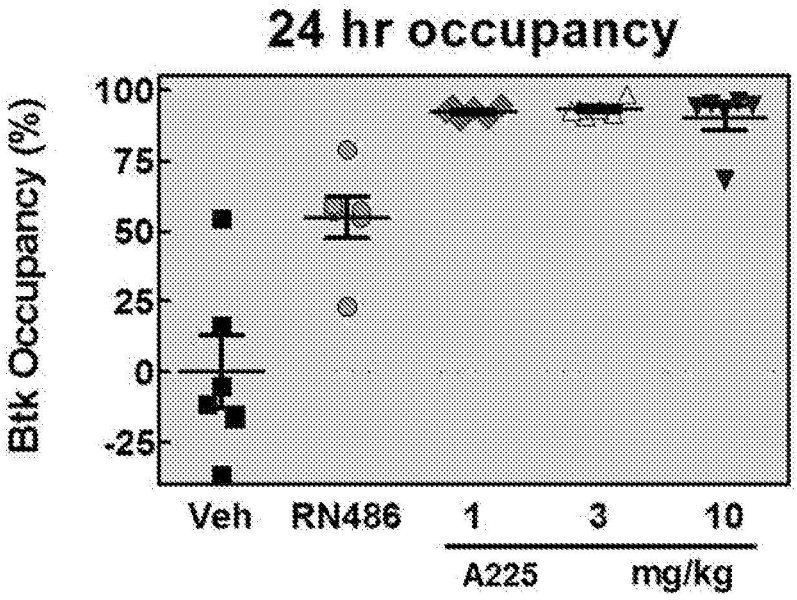


Figure 18 (a)

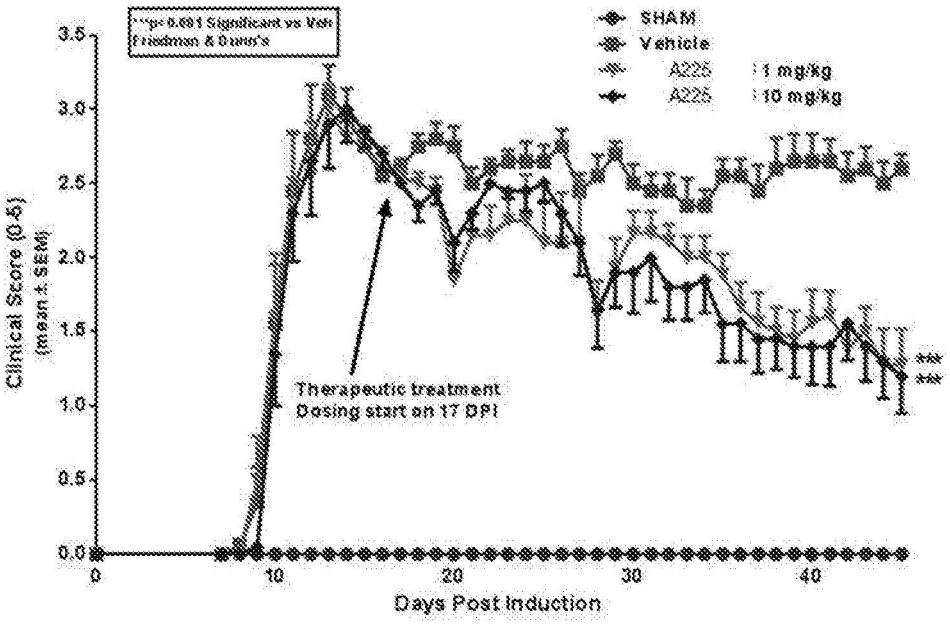


Figure 18 (b)

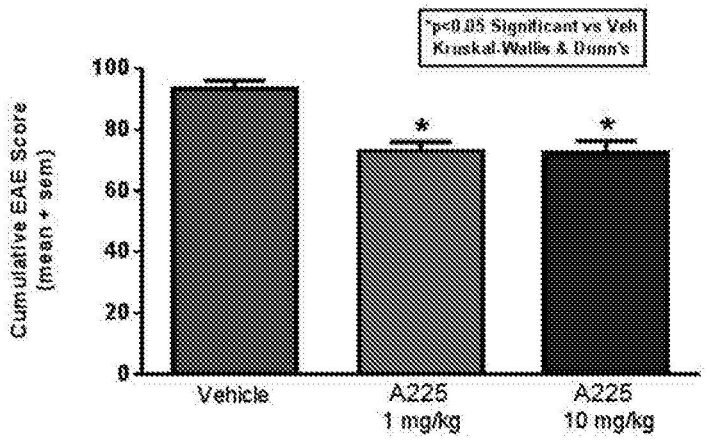


Figure 19 (a)

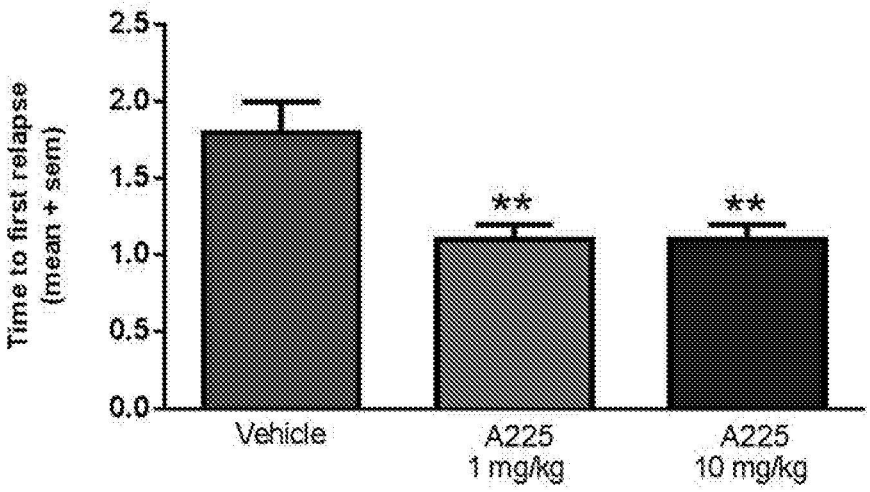


Figure 19 (b)

	1st RELAPSE (%)	2nd RELAPSE (%)
Vehicle	100	70
(A225) 1 mg/kg	100	10
(A225) 10 mg/kg	80	10

Figure 20 (a)

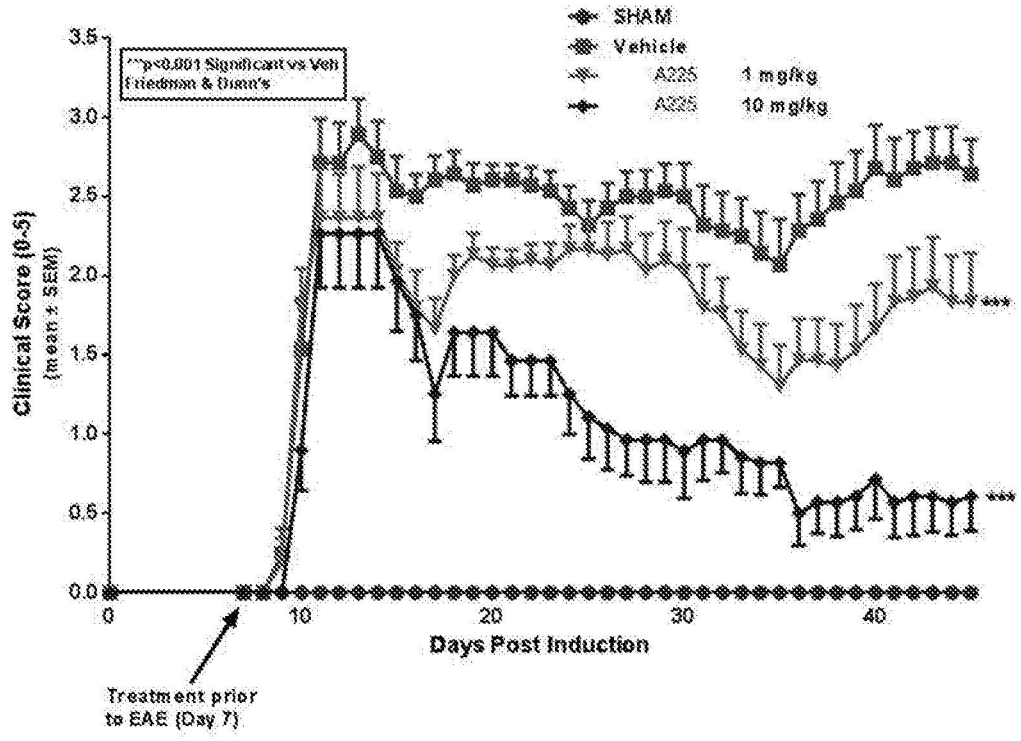


Figure 20 (b)

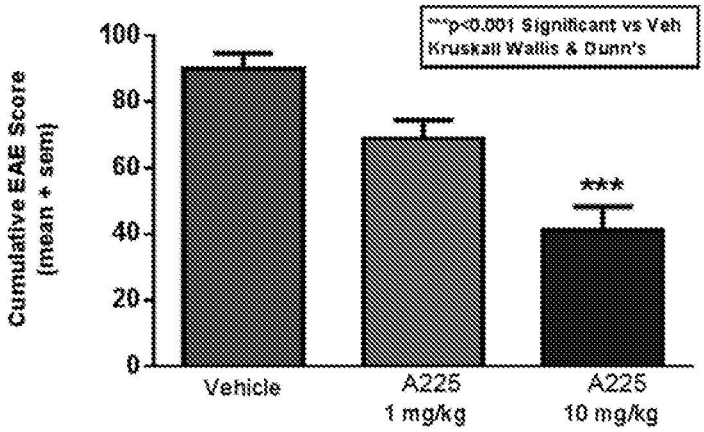


Figure 21 (a)

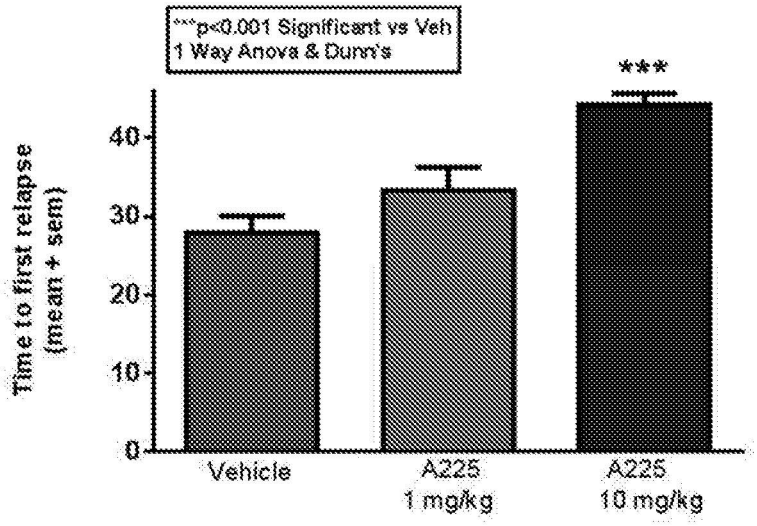


Figure 21 (b)

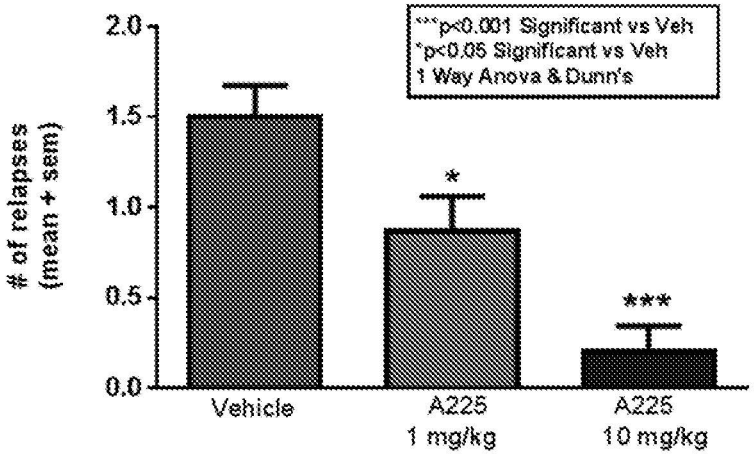


Figure 21 (c)

	1st RELAPSE (%)	2nd RELAPSE (%)
Vehicle	100	43
(A225) 1 mg/kg	67	20
(A225) 10 mg/kg	13	7