The novel sodium channel modulator GS-458967 (GS967) is an effective treatment in a mouse model of *SCN8A* encephalopathy

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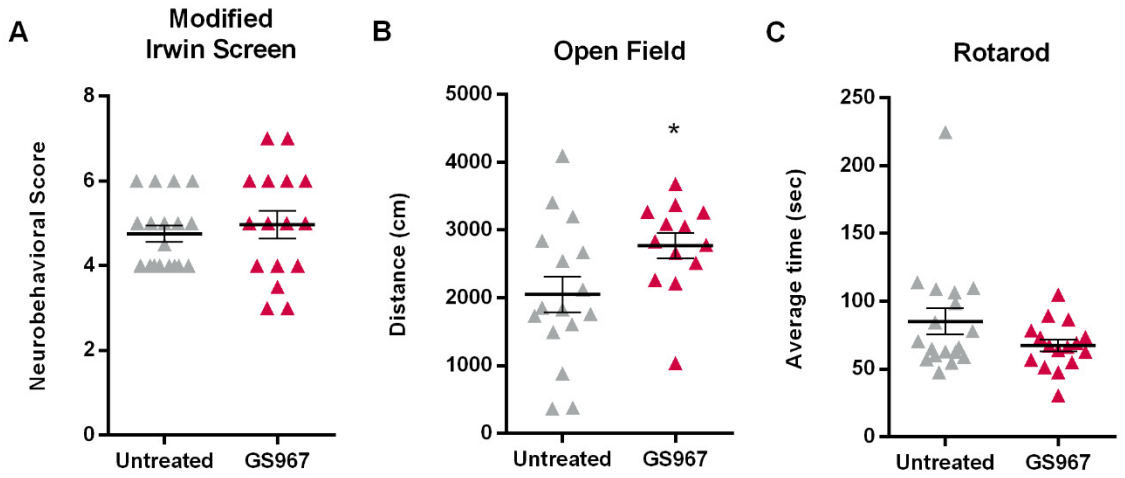
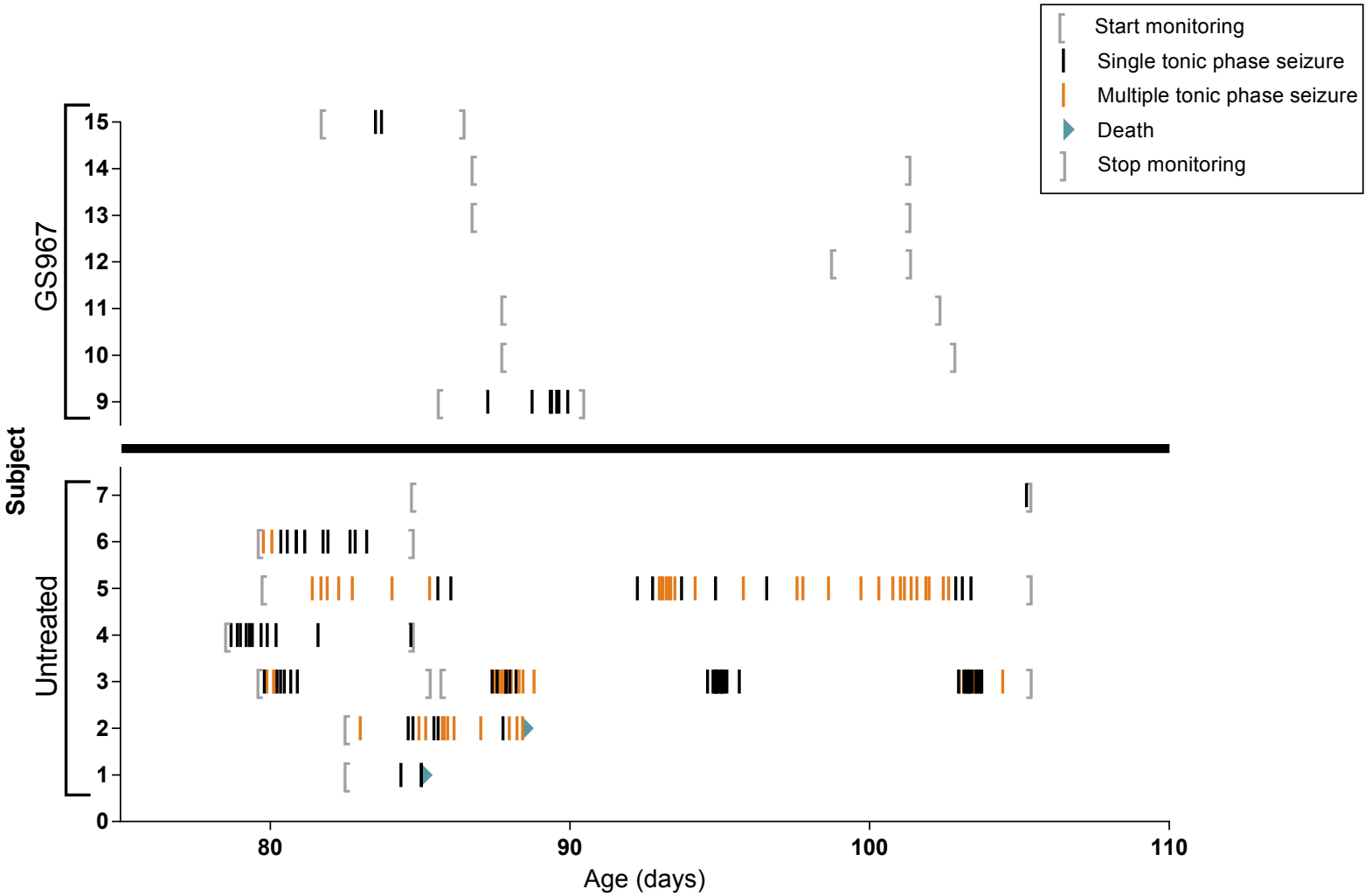
SUPPLEMENTAL INFORMATION



Supplemental Figure S1. Chronic treatment with GS967 for 5-7 weeks does not result in signs of neurobehavioral toxicity or sedation. At 6 weeks of age, WT C3HeB/FeJ mice were assigned to 1.5 mg/kg/day GS967 or control chow groups by block randomization. At 11-13 weeks of age, mice were tested in three assays on consecutive days. A, Modified Irwin screen conducted on day 1 showed no significant difference in neurobehavioral scores between GS967-treated and untreated control mice ($p > 0.05$; n = 16-18; Mann-Whitney test). Symbols represent mean ± S.E.M. B, Overall locomotor activity in an open-field was measured on day 2. GS967-treated mice showed a small, but significant increase in total distance traveled relative to untreated control mice, indicated by asterisk ($p < 0.05$; n=13-16; Student's t-test). C, On day 3 latency to fall from an accelerating rotarod showed no significant difference between GS967-treated and untreated control mice ($p > 0.05$; n = 16-17; Student's t-test).



Supplemental Figure S2. Seizure diary plot for *Scn8a*$^{D/+}$ mice undergoing continuous monitoring. Each line represents a single subject (1-7, Untreated; 9-15, GS967-treated). Black tick marks indicate a seizure event with a single tonic phase and orange tick marks represent seizure events with multiple tonic to tonic-clonic transitions. Recorded deaths are shown as triangles. Grey brackets indicate start and stop of continuous monitoring. Occasional brief monitoring gaps that account for <0.2% of total time (for husbandry or technical tasks) are omitted for presentation clarity. Seizure counts and calculated frequencies are summarized in Table 2.

Supplemental Table S1. Effects of GS967 on action potential (AP) parameters of WT and *Scn8a*$^{D/+}$ CA1 neurons.

	Threshold (mV)	**Rheobase (pA)**	**Input Resistance (mΩ)**	**Amplitude (mV)**	**Upstroke Velocity (mV/ms)**	**Downstroke Velocity (mV/ms)**	**AP Duration (ms)**
Untreated WT (n = 11)	-47.4 ± 0.7	125 ± 20	169 ± 14	97.9 ± 1.0	352 ± 14	-77.5 ± 3.1	1.1 ± 0.1
WT + GS967 (1 µM)	-45.5 ± 1.3	116 ± 20	183 ± 15	91.3 ± 2.1*	284 ± 15**	-75.7 ± 4.2	1.1 ± 0.1
Untreated *Scn8a*$^{D/+}$ (n = 13)	-43.9 ± 0.5$^{\#\#\#}$	173 ± 19$^{\#}$	149 ± 14	97.2 ± 1.4	344.4 ± 20	-54.4 ± 1.8$^{\#\#\#}$	1.4 ± 0.1$^{\#\#}$
Scn8a$^{D/+}$ + GS967 (1 µM)	-40.9 ± 1.1*	179 ± 26	140 ± 20	92.6 ± 2.7*	278 ± 22**	-50.4 ± 3.2	1.4 ± 0.1

Values represent mean ± SEM.

* Denotes statistical significance compared before and after GS967 treatment using paired t-test *p<0.05, **p<0.001

$^{\#}$ Denotes statistical significance compared between WT and Scn8a$^{D/+}$ using unpaired t-test. $^{\#}$p<0.05, $^{\#\#}$p<0.01, $^{\#\#\#}$p<0.001