

JBPOS0101:

**A New Generation mGluR- and BBB-
Targeted AED for the Treatment of
Super-Refractory Status Epilepticus (SRSE)**

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Who We Are

- **Bio-Pharm Solutions Co., Ltd.** is a privately-owned drug discovery and development company based in South Korea
- **Dr. Yong Moon Choi, CEO**, has a track record in the field of epilepsy, including orphan epilepsies:
 - Involved in the development of **Felbamate**, currently used in the treatment Lennox-Gastaut Syndrome
 - Invented **YKP3089**, currently in late-stage clinical development at SK for refractory partial-onset seizures
 - Invented **Carisbamate**, a drug candidate for refractory partial-onset seizures which reached the NDA stage

JBPOS0101 Overview of SRSE

- A unique mechanism of action (metabotropic glutamate receptors) not presently associated with currently-used antiepileptic drugs
- Potent efficacy in the pharmaco-resistant status epilepticus (BDZ-resistant)
- Antiepileptogenesis through suppressing spontaneous recurrent seizures
- Neuroprotection through blocking hemorrhages in the blood-brain barrier (BBB) of treatment-naive rats
- Potent anticonvulsant properties in a broad spectrum of epilepsy models
- Applications of JBPOS0101 go beyond orphan indications
 - JBPOS0101 has potential applications in infantile spasms based on preclinical pharmacology

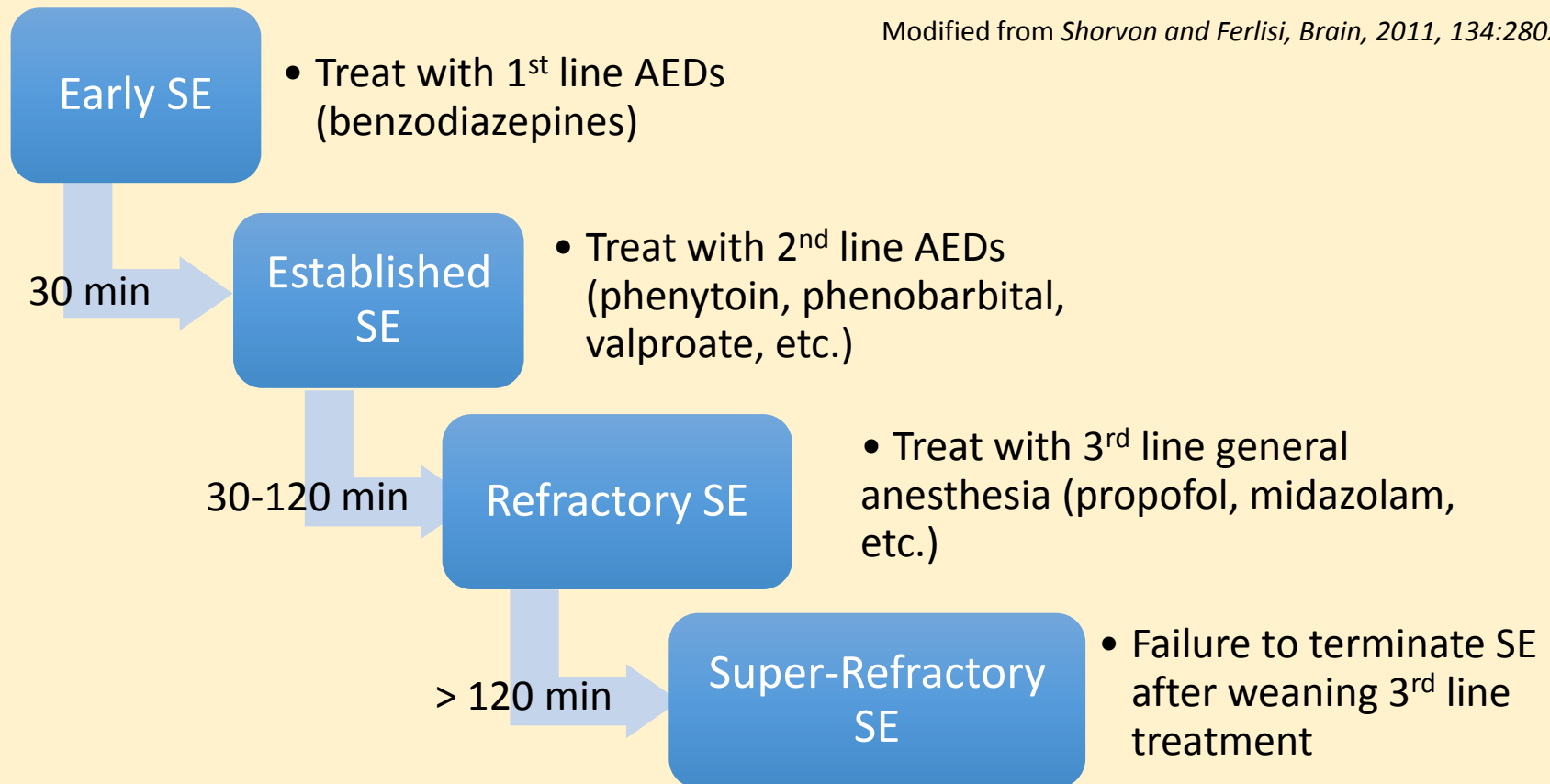
Prevalence of Status Epilepticus

- Reported to be between **20 - 40 / 100,000**
- Assuming a population of about 322,000,000, there are up to about **130,000 individuals** with status epilepticus in the United States
- An estimated **15%** of all cases of status epilepticus will become super-refractory*

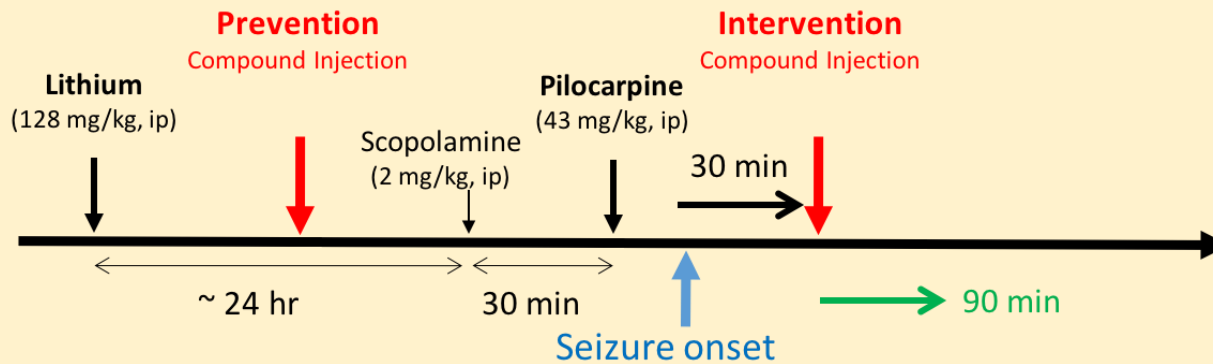
**Shorvon and Ferlisi, Brain, 2011, 134:2802-18*

Disease Overview: Super-Refractory Status Epilepticus

- Status epilepticus (SE) is defined as continuous seizure activity for ≥ 5 min
- One-third of patients with refractory and super-refractory SE will die, and another one-third will suffer chronic neurologic or other deficits
- No approved treatments for super-refractory SE at this time



JBPOS0101's Efficacy in Lithium-Pilocarpine-Induced SE

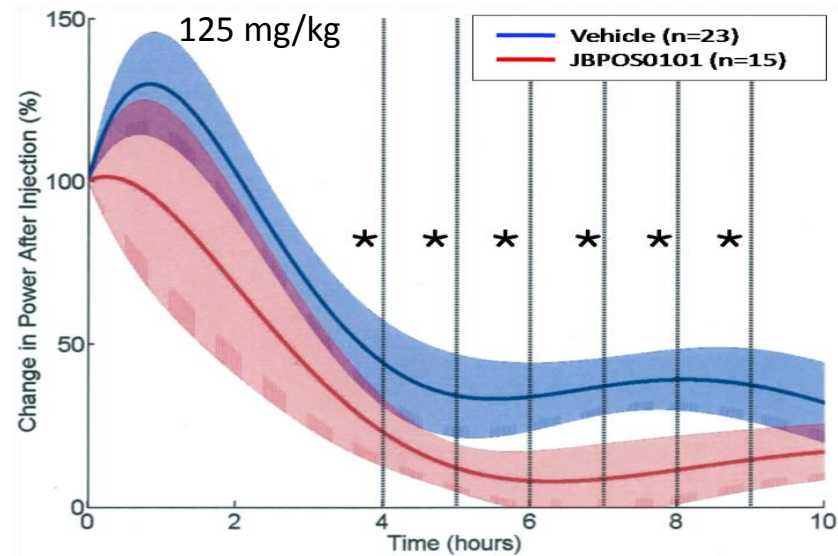
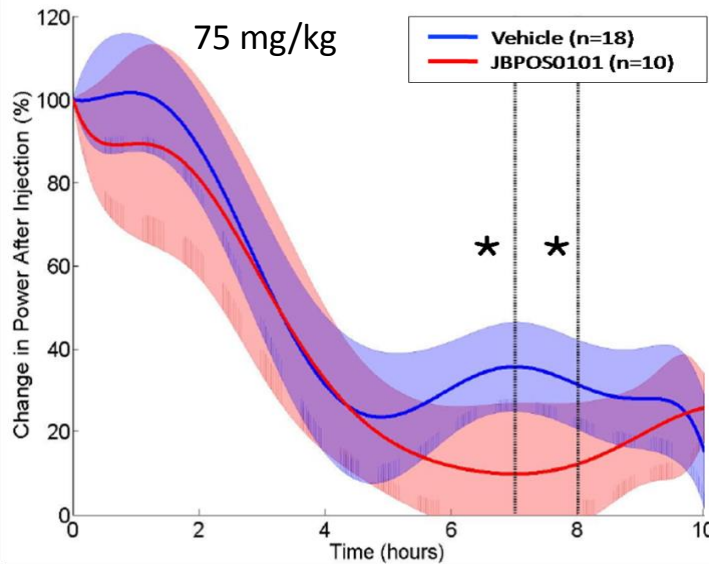
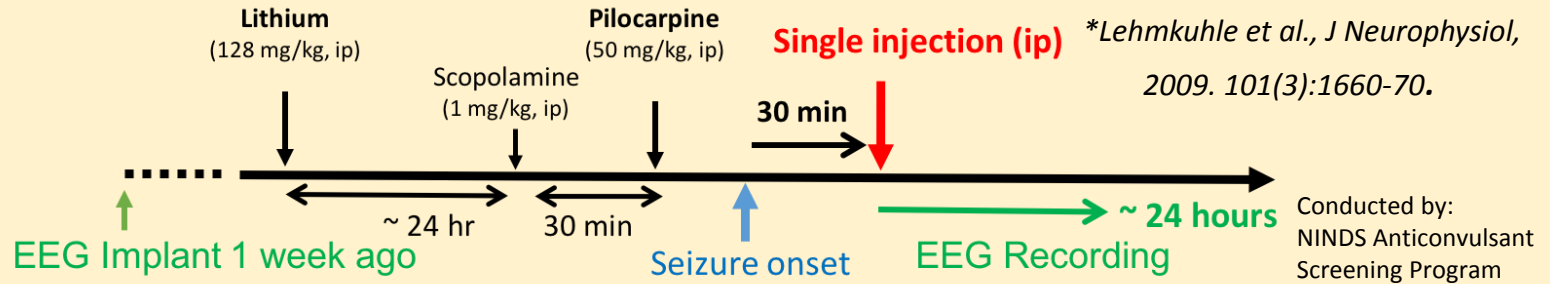


	Prevention	Intervention	Intervention (Benzodiazepine-resistant)	Intervention (Benzodiazepine-resistant)
JBPOS0101 injection Time	2 h before seizure induction	At seizure onset	30 min after seizure onset	30 min after seizure onset
Injection route	ip	iv	iv	ip
Observation time after seizure onset	90 min	90 min	90 min	90 min
ED ₅₀ (mg/kg)	19.1	20.4	54.3	80.4

JBPOS0101 shows potent efficacy in benzodiazepine-resistant SE

Efficacy of JBPOS0101 in Benzodiazepine-Resistant Electrographic SE

Benzodiazepine-resistant electrographic status epilepticus rat model:
Gamma wave power (20-70 Hz) on EEG for 10 hours



Solid line: mean, Shaded area: 95% confidence intervals, Mann-Whitney U-test, *p<0.05

JBPOS0101 suppresses benzodiazepine-resistant electrographic SE

Antiepileptogenic Effect of JBPOS0101 Following Benzodiazepine-Resistant SE

Monitoring of spontaneous recurrent seizures for 14 days

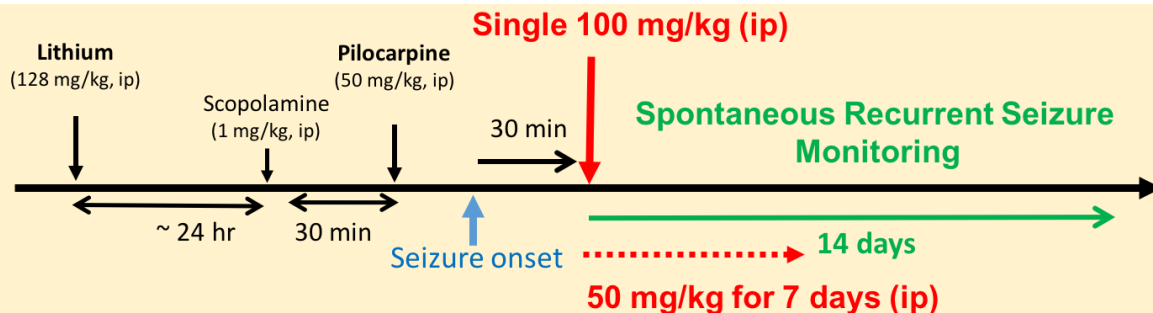


Table 1. The number of rats with seizures for 14 days.

(No. of rats with SRS's / No. of survived rats)

Day	Control	JBPOS0101	
		50 mg/kg 7days	100 mg/kg
Day 1	8 / 8	8 / 8	4 / 8
Day 2	5 / 7	7 / 8	3 / 8
Day 3	5 / 7	0 / 8	0 / 8
Day 4	5 / 7	0 / 8	0 / 8
Day 5	6 / 7	0 / 8	0 / 8
Day 6	3 / 7	0 / 8	0 / 8
Day 7	5 / 7	0 / 8	0 / 8
Day 8	3 / 7	2 / 8	0 / 8
Day 9	7 / 7	2 / 8	0 / 8
Day 10	3 / 5	1 / 8	0 / 8
Day 11	3 / 5	1 / 8	0 / 8
Day 12	3 / 5	1 / 8	0 / 8
Day 13	5 / 5	1 / 8	0 / 8
Day 14	4 / 4	1 / 8	0 / 8

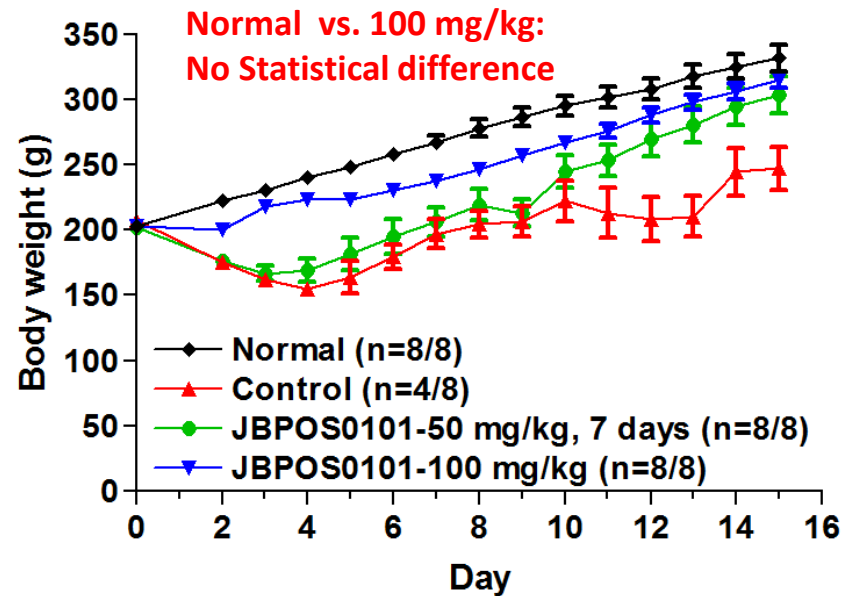
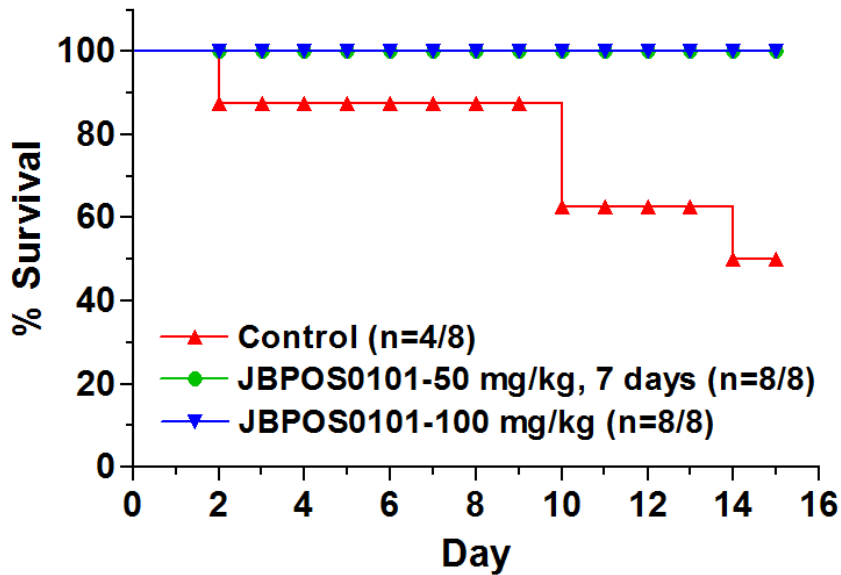
JBPOS0101 suppresses spontaneous recurrent seizures and shows evidence of antiepileptogenesis

Survival Rate and Body Weight in Lithium-Pilocarpine-Induced SE

Survival Rate and Change in Body Weight for 14 days

■ Survival rate

■ Body weight

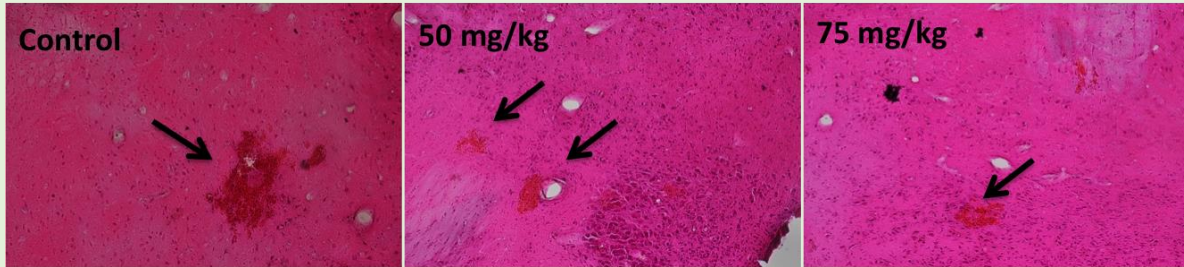


Data were represented as mean \pm S.E.M. Statistical analysis were performed by Two-way ANOVA test and followed Bonferroni Test as a *post hoc* analysis using Prism

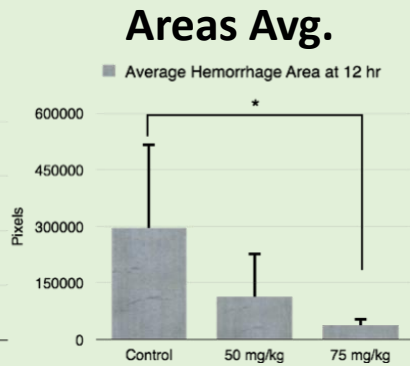
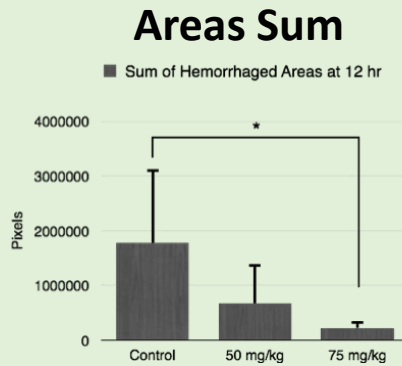
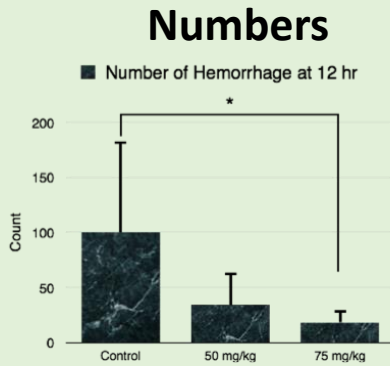
JBPOS0101 improves survival rate and body weight in SE

BBB Hemorrhages caused by Lithium-Pilocarpine-Induced SE

Examples of HE staining showing BBB hemorrhages

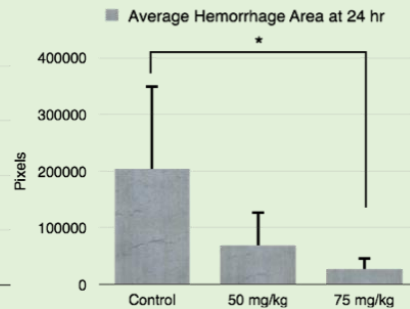
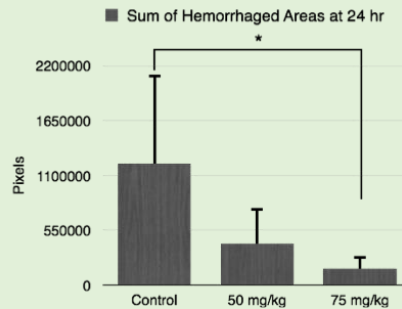
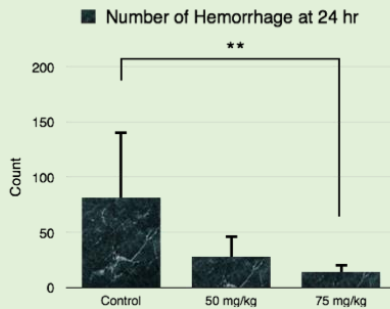


12 Hr



* $p < 0.05$,
 ** $p < 0.01$,
 10 – 12 brain sections/rat,
 n=6 for each group

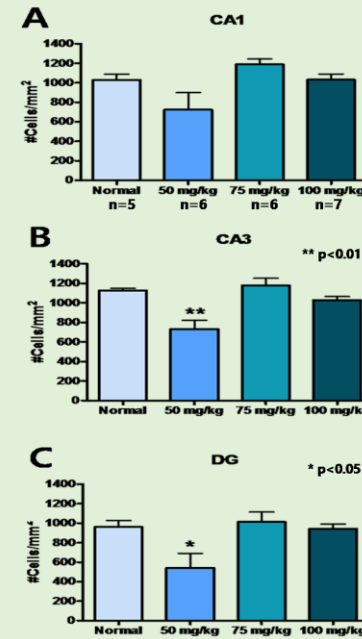
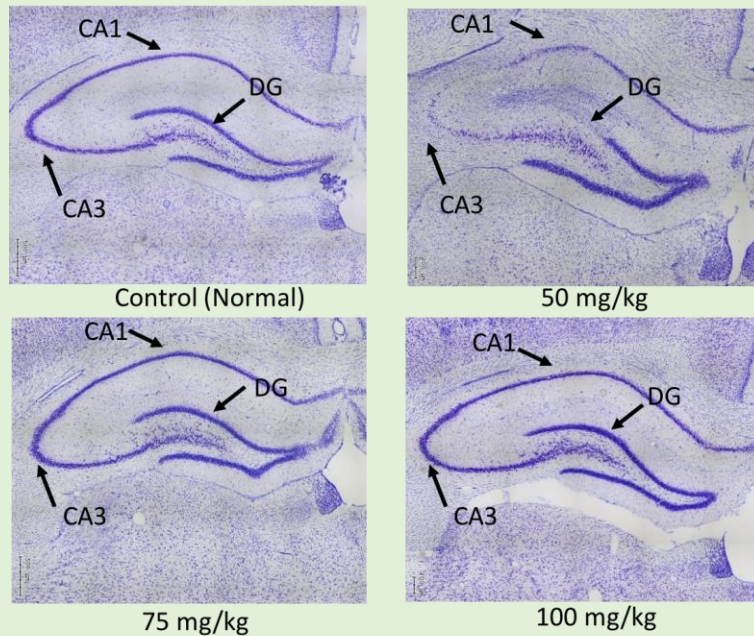
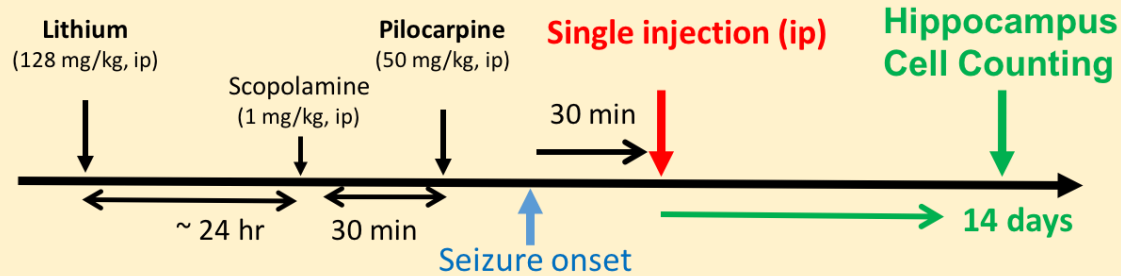
24 Hr



JBPOS0101 reduces the number and size of hemorrhages in the BBB caused by SE

Neuroprotective Effect of JBPOS0101 in Benzodiazepine-Resistant SE

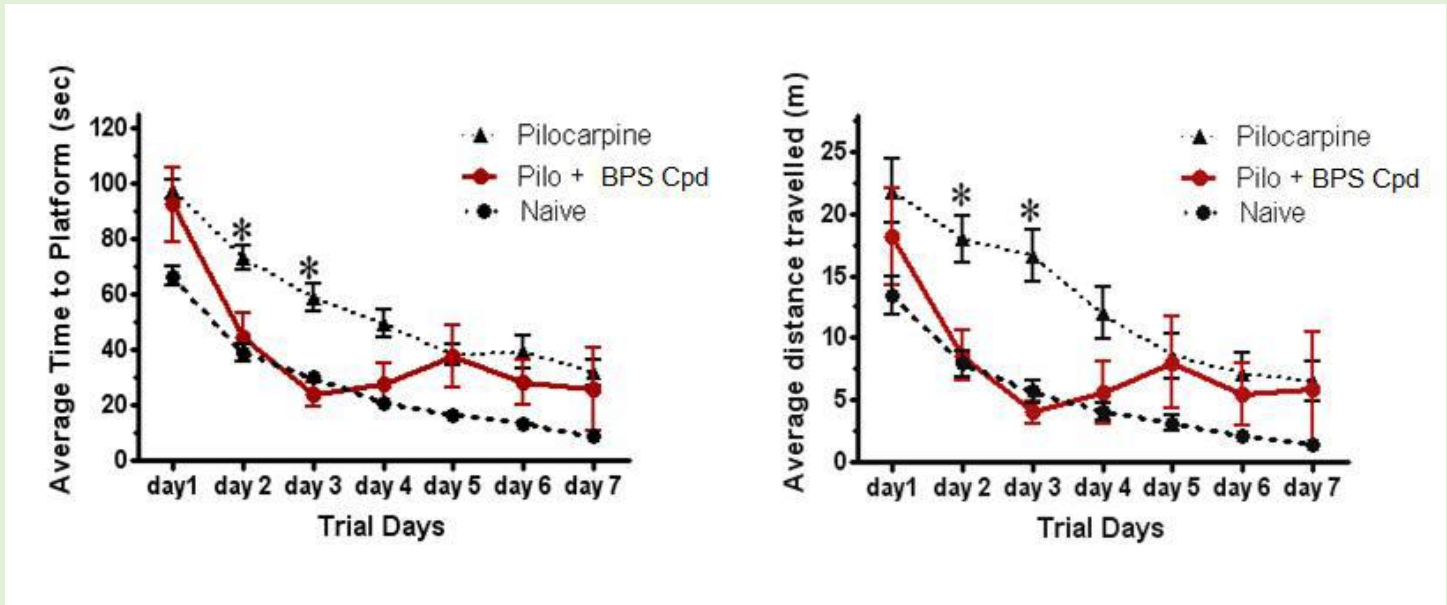
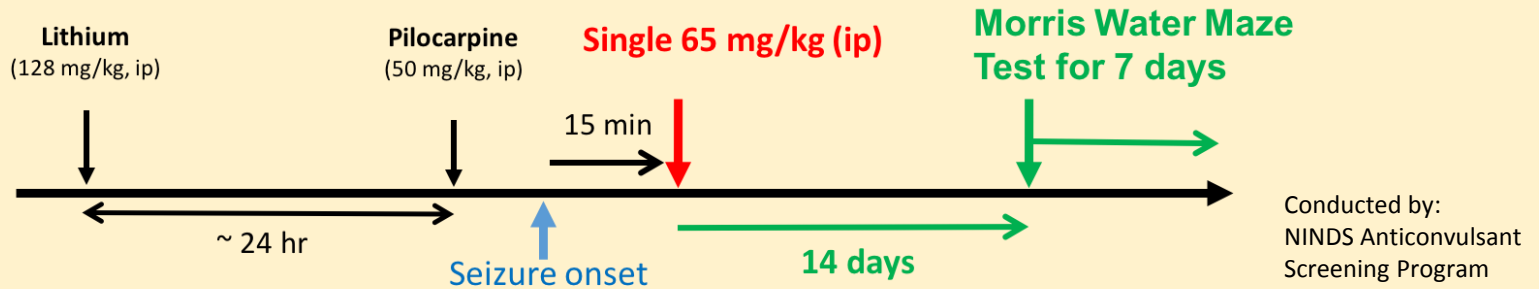
Status epilepticus-induced hippocampal cell loss after 14 days



JBPOS0101 protects hippocampus against status epilepticus-induced cell death

Effect of JBPOS0101 in SE-Induced Memory Deficits

Assessment of spatial memory and learning in SE-induced rats in the Morris Water Maze



Two-way ANOVA with Bonferroni's multiple comparison test, *p<0.05

JBPOS0101 improves spatial memory and learning functions in rats with SE

Comparison of Antiepileptic Activity in Animal Models

Compounds	ED ₅₀ (mg/kg)									
	Mice					Rats				
	MES (ip)	PTZ (ip)	scBIC (ip)	scPIC (ip)	Stry-Chnine (ip)	MES (po)	PTZ (po)	Li-Pilo Prevention (ip)	Li-Pilo Intervention (iv)	TD ₅₀ (po)
JBPOS0101	9.4 12.1 (po)	14.4	18.1	18.8	36.0	1.2	21.3	18	22.6	402.9 73-78 (ip)
Allopregnan-olone	>300	2.8 - 19	4.1	31.7	>300	>40	>10	6.8	5.8	27.3 (ip)
Levetiracetam	> 500	>500	4.7	>500	NA	>500	NA	NA	200 - 1200	>500
Phenytoin	5.64	>50	>50	>50	NA	28.1	>500	NA	NA	> 1000
Valproic acid	263	220	589	270	NA	485	646	NA	NA	784
Vigabatrin	> 1000	595	>2325	940	NA	NA	NA	NA	> 250 (ip)	NA
Lamotrigine	7.47	>40	>40	>40	54.3(po)	1.3	>412	NA	NA	411
Topiramate	33	>800	>500	>500	NA	15.8	>1000	>40	NA	>2000
Felbamate	35.5	126	>250	108	NA	25.3	NA	80.5	NA	>300
Pregabalin	20.0	109.0	250.0	250.0	NA	1.8	NA	NA	NA	NA

NA: Not Available

JBPOS0101 shows broad spectrum and potent efficacy

Phase 1 Trial:

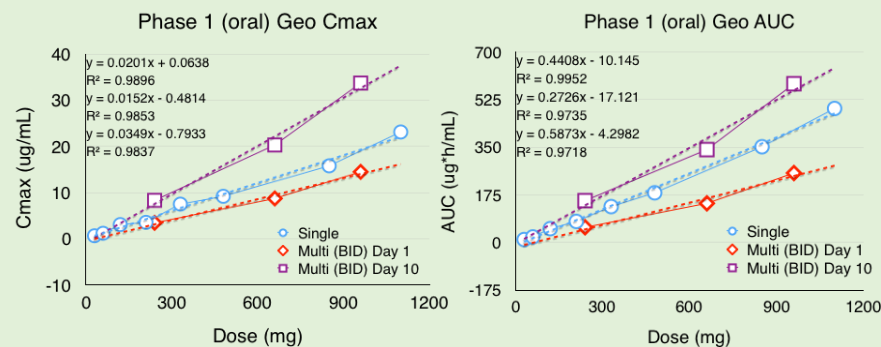
Safety, Tolerability, and PK in Young Healthy Subjects

• Phase 1 Protocol

- Approved by US FDA and Health Canada and conducted in Toronto, Canada
- Single Dose: 30 - 1100 mg, 64 subjects (8 subjects/8 groups, 6 active/2 placebo)
- Multiple Dose: 240 - 960 mg per day for 10 days, 24 subjects (8 subjects/3 groups, 6 active/2 placebo)

• Phase 1 Results

- No effects on vital signs
- PK data shows a dose-dependent linear relationship (C_{max}, AUC)
- Half-life ($T_{1/2}$) = 18 - 23 h
- Mild/transient adverse effects at the highest doses: headache, somnolence, dizziness, euphoria
- Very well tolerated by phase 1 volunteers



Summary

■ JBPOS0101

- New AED with novel mechanisms
- Active in models of pharmaco-resistant status epilepticus
- Evidence of antiepileptogenic & neuroprotective activity
- Broad spectrum of antiepileptic activity
- Other indications: neuroprotection, pain, anxiety, and depression

■ Current plan

- Super-refractory status epilepticus
 - Phase II study (open-label, single-center, adjunctive therapy)
 - Will be performed in USA and South Korea
 - Phase II study initiation in 2017
- Infantile spasms
 - Protocol development/US FDA meeting preparation in progress
- ✓ Response to treatment can be assessed quickly for both clinical trials