# The Efficacy of a Dual-Acting, Peripherally-Restricted kappa/delta Opioid Agonist (CAV1001) in Neuropathic Pain in the Rat

## Background

Nerve injury can precipitate a neuroimmune inflammatory response.<sup>1</sup> This response might lead to the activation of peripheral delta opioid receptors, allowing delta opioid agonists in the periphery to become analgesic directly and through allosteric modulation of peripheral kappa opioid receptors.<sup>2</sup>

### Purpose

This study evaluated the efficacy of a single intraperitoneal injection of CA1001 (a novel peripherally-restricted dualacting *kappa/delta*-opioid agonist) and the comparator, gabapentin, in the spinal nerve ligation (SNL) model for neuropathic pain in the rat.

### Methods

- Following IACUC approval, neuropathy was induced by surgically ligating the 5th and 6th lumbar spinal nerves (L5 and L6);
- Mechanical sensitivity was assessed via paw compression thresholds (PCTs) using a digital Randall-Selitto device;
- 50 animals that met the inclusion criteria were randomly assigned to 5 groups with 10 animals per group (Power: 80%);
- Animals were administered a single dose of vehicle, CAV1001 (1 mg/kg, 5 mg/kg, or 10 mg/kg IP), or control compound (gabapentin 100 mg/kg PO; active control: internal validity) on day 0 (15 days after SNL) and PCTs were determined 1, 2, and 4 hours after compound administration;
- All behavioral evaluations were performed by a blinded observer.

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### Study Design: Neuropathic Pain (SNL)

Test Syste	System ID: Species: Breed: Sex Rat: Sprague-Dawley: Male					
Group #	Treatment	N	Dose (mg/kg)	Vol. (mL/kg)	Route	Day of Admin/ Frequency
1	Vehicle (Ethanol: Tween 80: Normal Saline – 1:1:8)	10	N/A	5	IP	Day 0 / 1x
2	CAV1001	10	1	5	IP	Day 0 / 1x
3	CAV1001	10	5	5	IP	Day 0 / 1x
4	CAV1001	10	10	5	IP	Day 0 / 1x
5	Gabapentin	10	100	5	IP	Day 0 / 1x

## Results

### Neuropathic Pain: Hyperalgesia Development

Unpaired t-test, two-tailed, Ipsilateral vs. Contralateral								
Time Point	t	Df	p-Value					
Pre-Injury Baseline	0.6803	18	0.505					
Pre-Dosing Baseline	4.59	18	0.0002					
1 Hour	6.542	18	<0.0001					
2 Hour	4.098	18	0.0007					
4 Hour	7.304	18	<0.0001					

Gabapentin significantly reversed SNL-induced mechanical hyperalgesia at 1, 2, and 4-hours (p<0.01 versus vehicle, t test).



- CAV1001 at the 1 mg/kg dose did not significantly reverse mechanical hyperalgesia at any of the time points tested;
- The 5 mg/kg and 10 mg/kg doses of CAV1001 did not significantly reverse mechanical hyperalgesia at the 1-hour post-dosing time point but did significantly reverse mechanical hyperalgesia at the 2-hour (p<0.05 versus vehicle by one-way ANOVA) and 4-hour (p<0.001 versus vehicle by one-way ANOVA) post-dosing time points.

# Conclusion The reversal of mechanical hyperalgesia by CAV1001 at 5 mg/kg and 10 mg/kg did not differ significantly from the active control, gabapentin. References <sup>1</sup>Totsch SK, Sorge RE. Immune system involvement in specific pain conditions. Molecular Pain. 2017;13:1-17. <sup>2</sup>Brackley AD, Gomez R, Akopian AN, Henry MA, Jeske NA. Cell Rep. 2016; 16(10): 2686–2698.

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