# Reversal of Mechanical Hyperalgesia by a Dual-Acting, Peripherally-Restricted kappa/delta Opioid Agonist (CAV1001) in a Rat Model of Inflammatory Arthritis

Craig T. Hartrick, MD, FIPP<sup>1</sup>, Rebekka Molenaar, MS<sup>2</sup>, Jim Pomonis, PhD<sup>2</sup>, Allison Hartrick, MBA<sup>1</sup>

(1)Caventure Drug Discovery, (2)American Preclinical Services

## Background

Rheumatoid arthritis (RA) is a chronic inflammatory pain condition. In RA and other inflammatory states, normally sequestered peripheral *delta* opioid receptors may become active, allowing *delta*-opioid agonists to participate in the pain pathway directly and through allosteric modulation of peripheral *kappa* opioid receptors.<sup>1</sup>

### Purpose

This study evaluated the efficacy of a single intraperitoneal injection of CAV1001 (a novel dual-acting, peripherally restricted *kappa/delta* opioid agonist) on hyperalgesic nociceptive behaviors in the CFA (Complete Freund's Adjuvant) Model of Inflammatory Arthritis Pain in Rats.

#### Methods

- Following IACUC approval, inflammatory arthritis pain was induced with injection of 50 µL CFA into the tibio-tarsal joint;
- Mechanical hyperalgesia was assessed via joint compression thresholds (JCTs);
- 50 animals were randomly assigned to 5 groups (Power: 80%);
- Ipsilateral and contralateral joint compression thresholds (JCTs) were assessed prior to CFA injection, pre-dosing on Day 0, and 1, 2, and 4 hours post-dosing;
- Animals were administered a single dose of vehicle, CAV1001 (1, 5, or 10 mg/kg IP), or celecoxib (30 mg/kg PO: active control; internal validity) on day 0 (14 days after CFA);
- All behavioral evaluations were performed by a blinded observer;
- Mechanical hyperalgesia was measured using a digital Randall
   Selitto device.

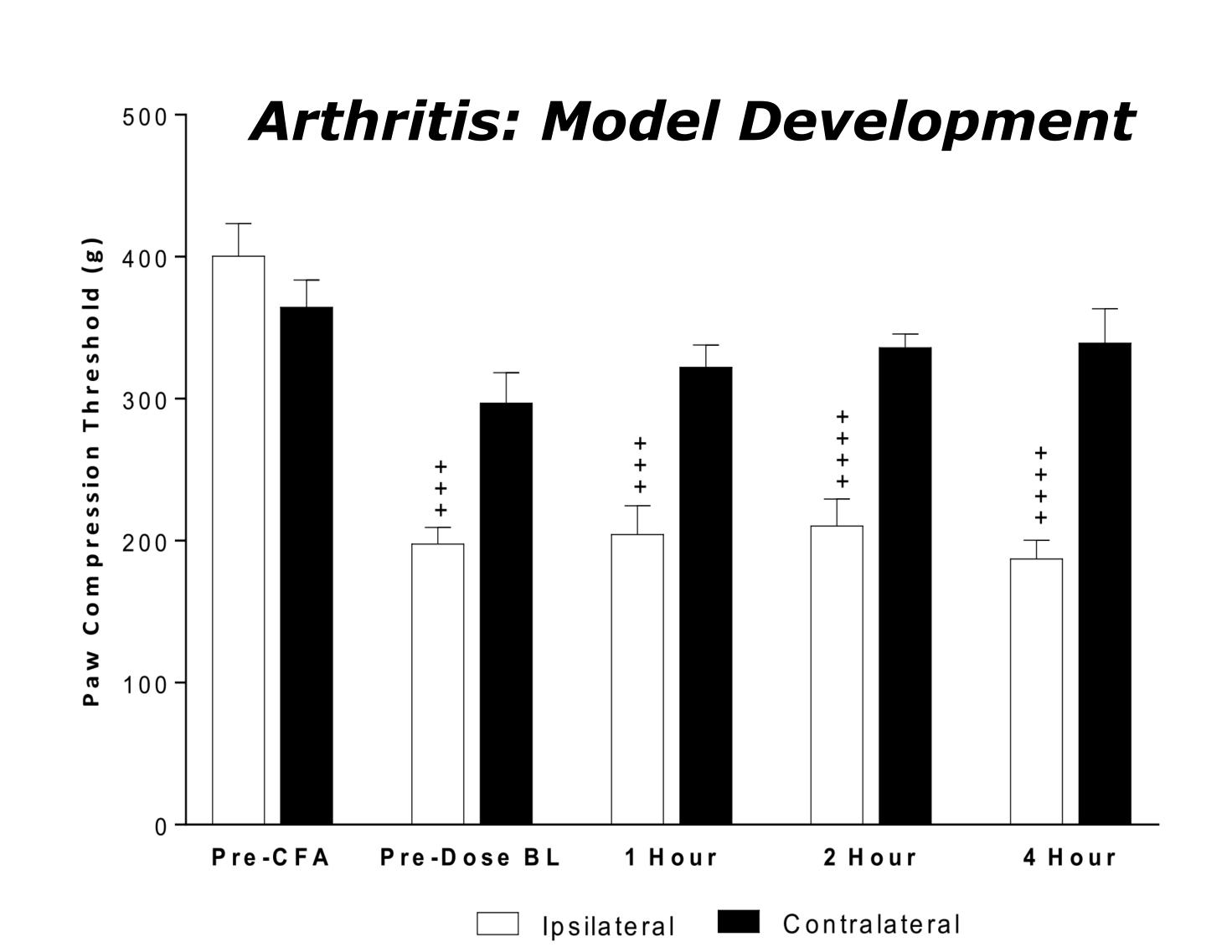
#### Study Design: Arthritis (CFA Ankle)

Test 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	Celecoxib	10	30	5	РО	Day 0 / 1x

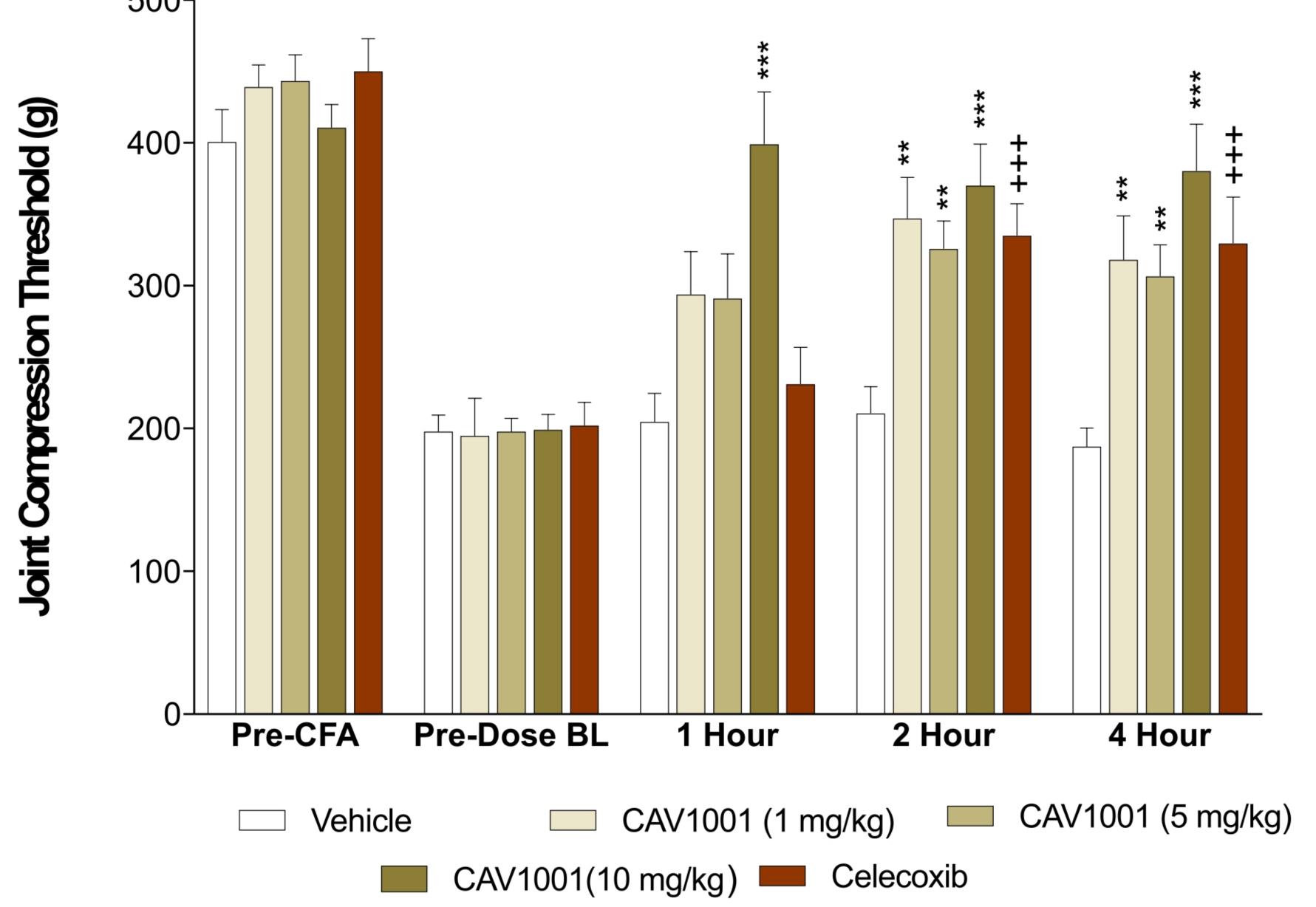
#### Results

#### Arthritis: Hyperalgesia Development

Unpaired t-test, two-tailed, Ipsilateral vs. Contralateral								
Time Point	t	Df	p-Value					
Pre-Injury Baseline	1.22	18	0.240					
Pre-Dosing Baseline	4.11	18	0.0007					
1 Hour	4.66	18	0.0002					
2 Hour	5.98	18	<0.0001					
4 Hour	5.56	18	<0.0001					



# Arthritis: Results



+++: p<0.001 (t test);

\*\*: p<0.01 (one-way ANOVA);

\*\*\*: p<0.001 (one-way ANOVA)

- CAV1001 (10 mg/kg) significantly increased paw compression thresholds compared to vehicle at all time points, (p<0.001, one-way ANOVA);
- CAV1001 (1 mg/kg and 5 mg/kg) significantly improved paw compression thresholds at both the 2-hour and 4-hour time points (p<0.01, one-way ANOVA);
- Celecoxib did not significantly improve thresholds at 1 -hour but did at the 2-hour and 4-hour time points (p<0.001, t test).

#### ++: p<0.001; +++: p<0.0001 (t tests)

#### Conclusion

Intraperitoneal administration of CAV1001 significantly reversed CFA-induced mechanical hyperalgesia. The reversal in mechanical hyperalgesia with CAV1001 1 mg/kg was comparable to the active control, celecoxib.

#### Reference

<sup>1</sup>Brackley AD, Gomez R, Akopian AN, Henry MA, Jeske NA. Cell Rep. 2016; 16(10): 2686–2698.

#### Contact

Dr. Craig T Hartrick chartrick@caventuredrugdiscovery.com

Allison Hartrick ahartrick@caventuredrugdiscovery.com

