Osteoarthritis Oral Phase 2a Study

CR845-CLIN2001-PO

A Single-Blind, Multiple Ascending-Dose Pilot Study of the Safety, Tolerability, Pharmacokinetics, and Effectiveness of Orally Administered CR845 in Patients with Osteoarthritis of the Hip or Knee

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CLIN2001: Protocol Overview

Main Objective:

- Assess the safety and tolerability of orally-administered CR845 in patients with osteoarthritis (OA) of the hip or knee
- Characterize the PK profile of orally-administered CR845 with b.i.d. dosing
- Explore the effectiveness of orally-administered CR845 in this patient population

Study Design:

- Single-Blind, Multiple Ascending-Dose Phase 2a Study, with repeat doses of CR845 over a two-week period in patients with moderate-to-severe pain (≥ 4) associated with OA
- Four treatment arms; oral b.i.d. doses: 0.25mg, 0.5mg, 1mg & 5mg tablets

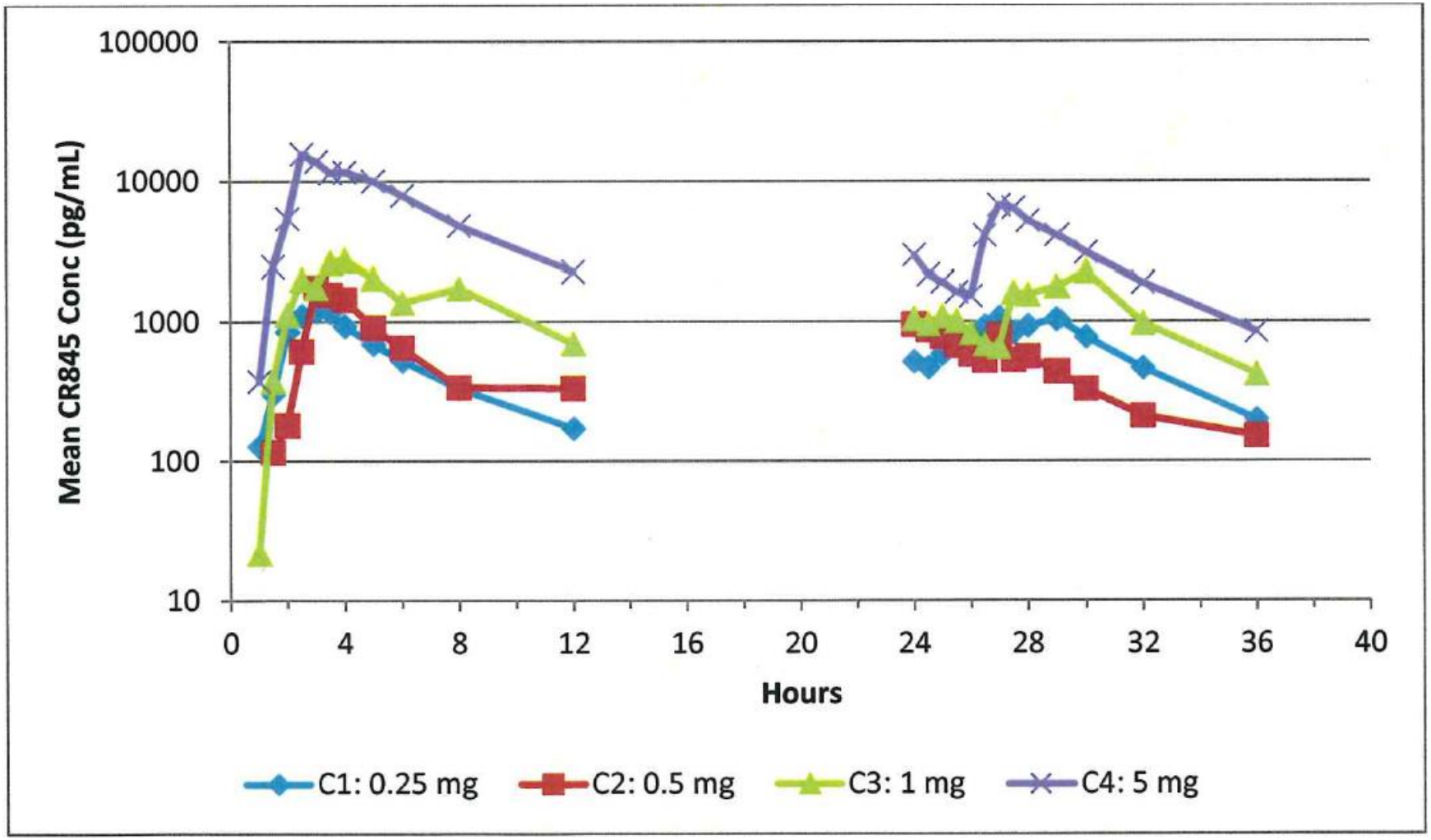
Patients:

- 80 male and female patients – 20/treatment arm (baseline NRS ≥ 4), 5 U.S. sites
- Mean patient OA duration at screening – 9.4 years

Study CR845-CLIN2001-PO
Patient Demographics

	Cohort 1 0.25mg (n= 20)	Cohort 2 0.5mg (n= 21)	Cohort 3 1.0mg (n= 20)	Cohort 4 5.0mg (n= 20)
Gender				
Male	10 (50%)	14 (66.7%)	8 (40%)	11 (55%)
Female	10 (50%)	7 (33.3%)	12(60%)	9 (45%)
Age, mean (range)	63.2 (46-77)	63.3 (32-80)	62.9 (38-81)	63.1 (40-79)
Race				
Black	5 (25%)	4 (19%)	1 (5%)	5 (25%)
White	15 (75%)	17 (81%)	19 (95%)	15 (75%)
Ethnicity				
Hispanic or Latino	0 (0%)	1 (4.8%)	1 (5%)	0 (0%)

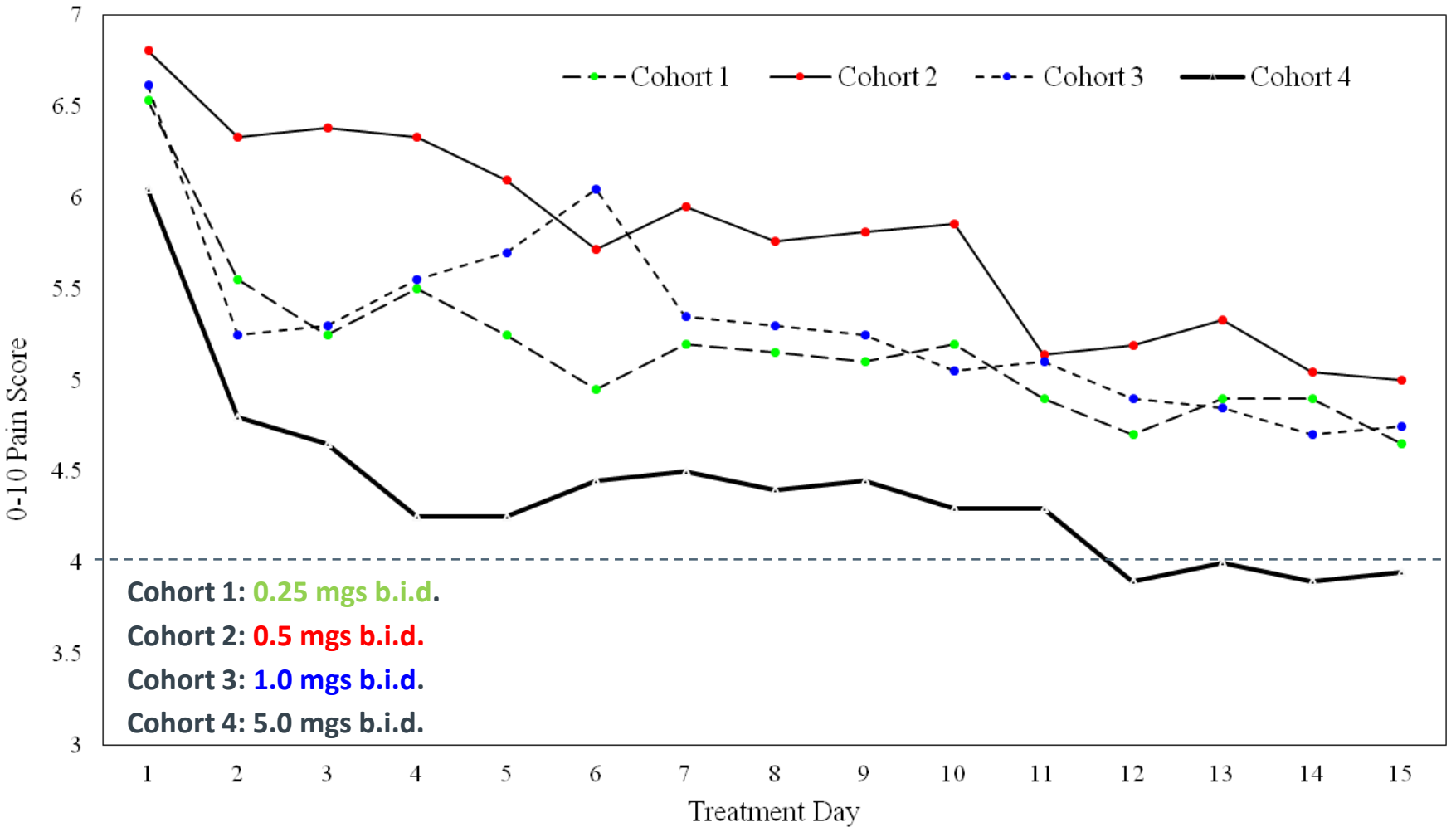
Study CR845-CLIN2001-PO
CR845 Plasma Concentration



Study CR845-CLIN2001-PO Safety/Tolerability Summary

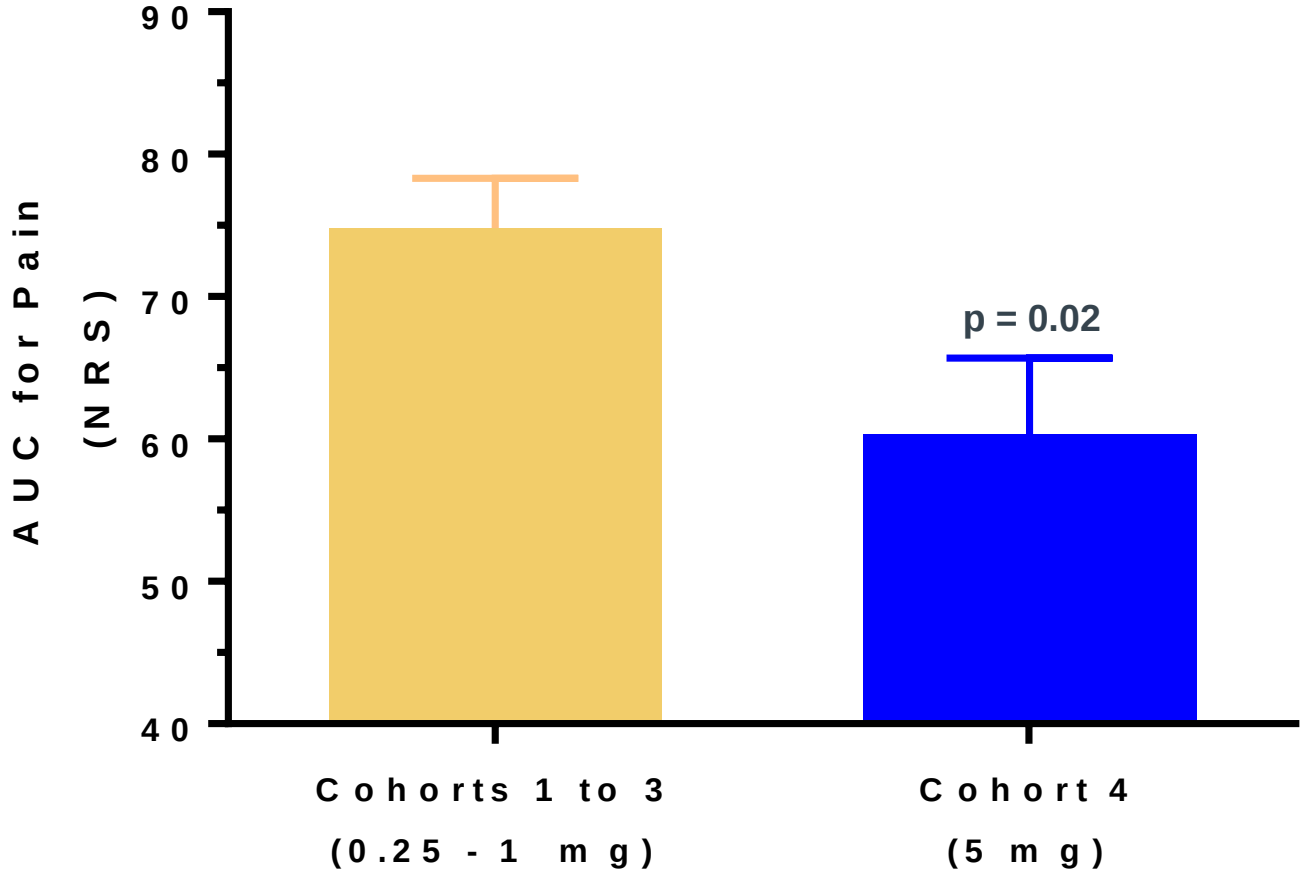
- 65% of reported events characterized as mild, remainder moderate & no severe
- Dose-dependency to AEs – 20% in high (5mg) group
- Treatment-related AEs with >5% incidence:
  - Dizziness (7%)
  - Headache (6%)
- One study SAE – status epilepticus (non-drug related)

Study CR845-CLIN2001-PO:
Mean NRS Score by Cohort and Treatment Day – LOCF

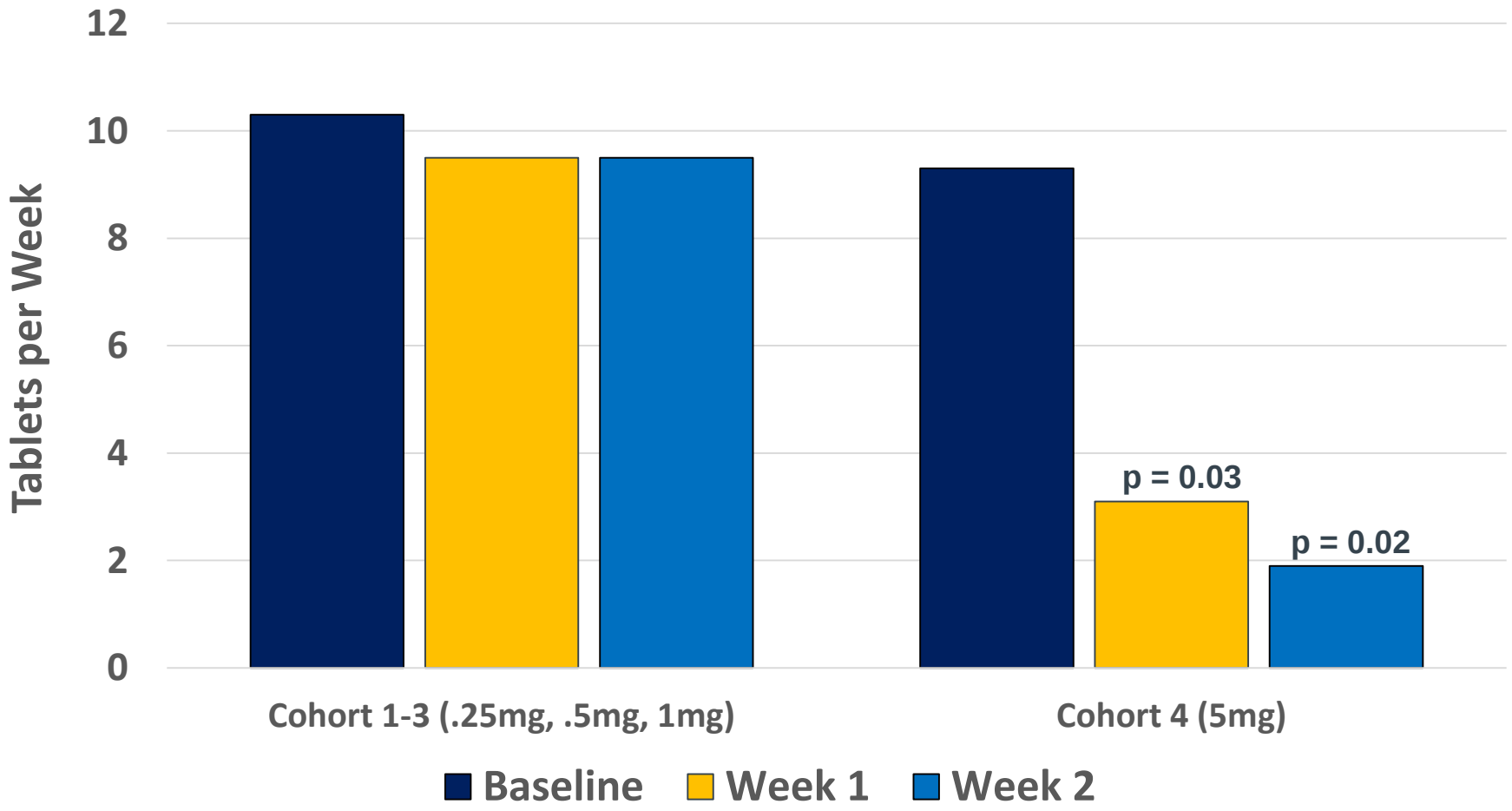


LOCF analysis

Study CR845-CLIN2001-PO:
Area Under the Curve (AUC), Pain NRS, Days 1 to 15

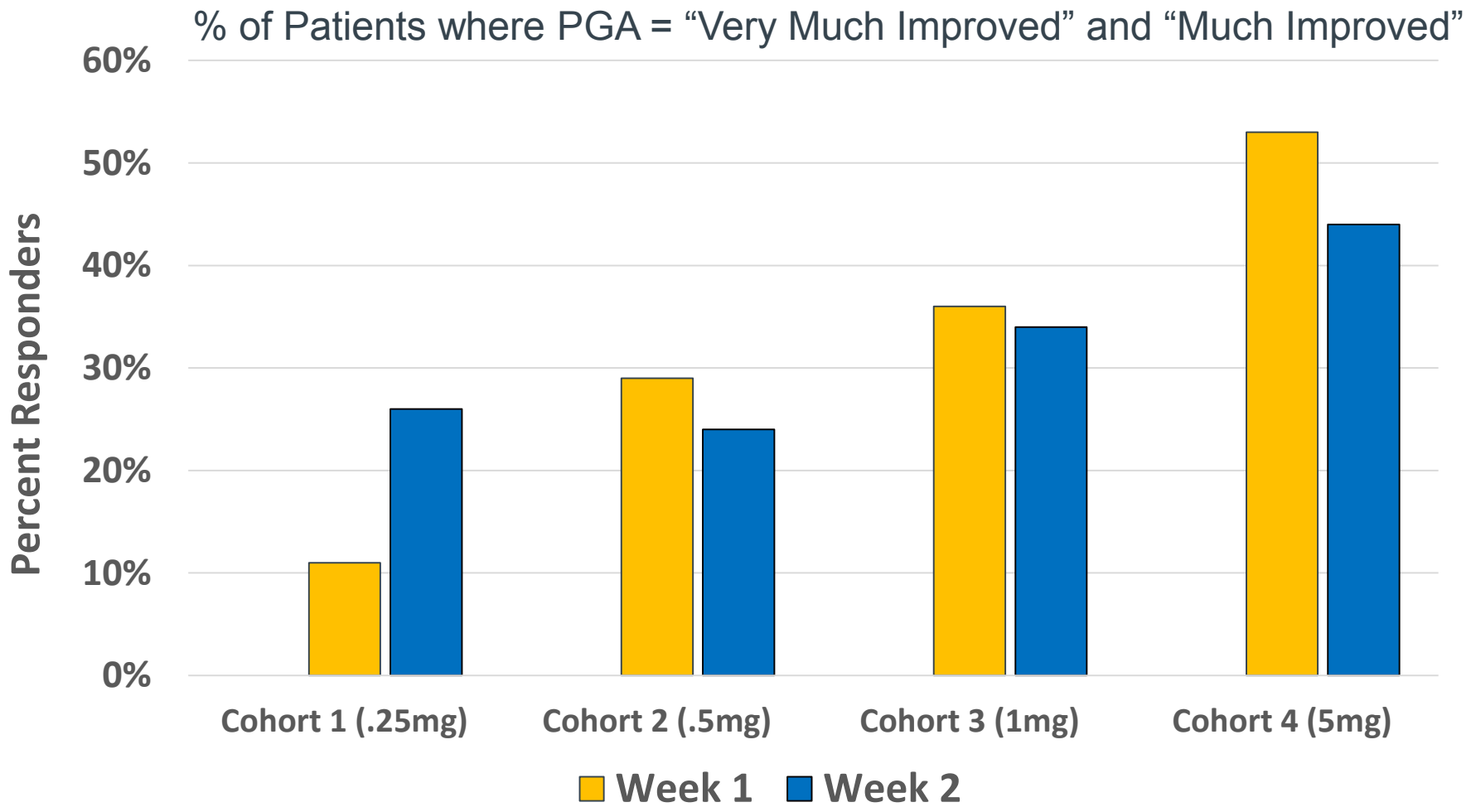


Study CR845-CLIN2001-PO: Rescue Medication Use over Time



59% of patients in Cohort 4 (5mg) did not require any rescue medication.

Study CR845-CLIN2001-PO: Patient Global Assessment (PGA)



Comparative Efficacy in NRS Pain in OA Studies

Drug	Time	Change from BL	% Change from BL
Naproxen[1]	2 weeks	-2.5	35%
Celecoxib[1]	2 weeks	-2.5	35%
Duloxetine[2] (30mg/day)	2 weeks	-1.6	26%
Oxycodone CR[3]	12 weeks	-1.7	26%
CR845 (1mg)	2 weeks	-1.7	26%
CR845 (5mg)	2 weeks	-2.1	34%

1. Benson, et. al. Treatment of Osteoarthritis with Celecoxib, a Cyclooxygenase-2 Inhibitor: a Randomized Controlled Trial. *Mayo Clin Proc. 1999;74:1095-1105*
2. Chappell et. Al., Duloxetine, a centrally acting analgesic, in the treatment of patients with osteoarthritis knee pain: A 13-week, randomized, placebo-controlled trial. *PAIN.* Volume 146, Issue 3, 5 December 2009, Pages 253–260.
3. Markenson, et. al., Treatment of Persistent Pain Associated With Osteoarthritis With Controlled-Release Oxycodone Tablets in a Randomized Controlled Clinical Trial. *Clin J Pain* Volume 21, Number 6, November/December 2005.

CARA THERAPEUTICS

Oral CR845 Osteoarthritis: Next Steps

- Phase 2b trial: 1mg-5mg tablet range, b.i.d.
  - 6 weeks treatment period
  - Double-blind, placebo-controlled
  - ~15 U.S. sites
- Initiate Phase 2b Trial – 1'H 2016