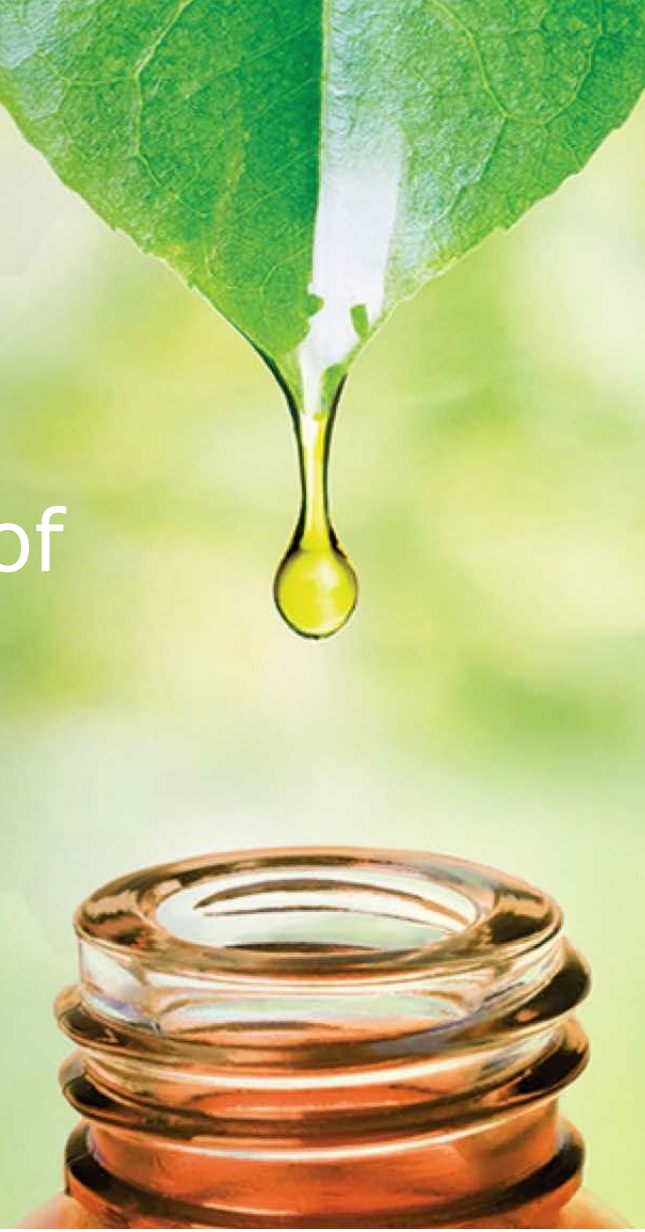
The Development of Proprietary High-strength Topical Capsaicin Formulations for the Treatment of Osteoarthritis (OA) Pain



13th Annual Pain Therapeutics Summit

September 23, 2019

Vizuri HEALTH SCIENCES

Vizuri Health Sciences LLC

Founded by visionaries:

Charles Birbara, MD (Rheumatologist, UMass Med School)

Philip Birbara, PhD (ACS Hero of Chemistry Award, NASA)

Milt Peterson (The Peterson Companies)

Dedicated to the discovery and application of formulation technologies to pharmaceutical product development

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Vizuri HEALTH™ SCIENCES

*OA in the United States

- **Arthritis**
  - 31 Million US adults have osteoarthritis (OA) and incidence is increasing
    - Third most common primary care diagnosis in older patients and the fifth most costly
- **Knee pain**
  - 25% of those over 55 years of age experience persistent knee pain
  - 33% of older adults in the general population have radiographic evidence of knee OA
  - 50% of older adults with knee pain report some restriction of daily activity
- **Treatment landscape**
  - On average, there is a 17-month lag between OA diagnosis and knee replacement surgery
  - Apart from joint replacement, therapies do not effectively manage disease progression
    - **Pain management is key**

*According to the Arthritis Foundation

Why Topical Capsaicin for Management of OA Pain?

- **Efficacy**
  - Repeat exposure of nociceptor TRPV-1 to capsaicin results in neurotransmitter depletion and a reduction in the number of epidermal nerve fibers that transmit pain
  - Reinnervation to baseline may take weeks to months, thereby providing durable responses
- **Safety**
  - No addiction potential (unlike opioids)
  - Very low systemic risk; no capsaicin-related SAE or DDI concerns (unlike NSAIDs)
  - Suppression of nociceptor function blocks 50–70% of sensory nerve signaling, not 100%
  - The major AE is burning, stinging pain (BSP) at the administration site
    - BSP typically rated as mild to moderate, not severe, pain
    - BSP decreases with subsequent administration within treatment
  - No pretreatment with analgesics or cooling as is required with other Rx capsaicin products
    - Allows for patient self administration

Topical Capsaicin Proven Effective for Knee OA Pain

Recommended by the American College of Rheumatology for Knee and Hand OA Pain

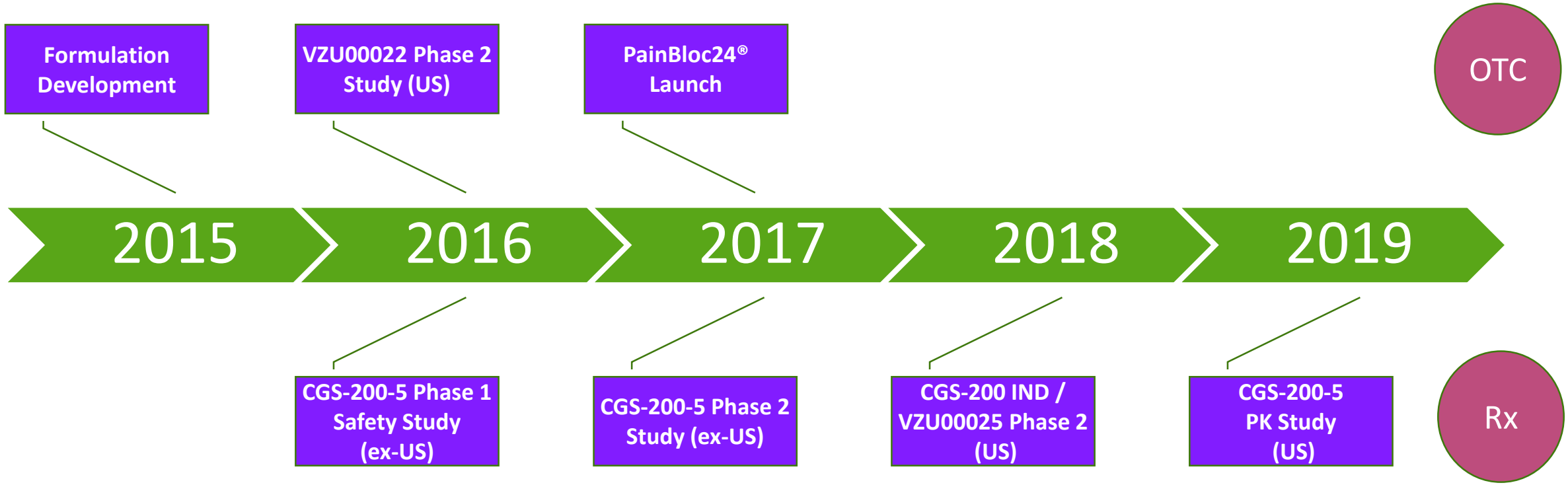
Study Reference	Design	Efficacy	Safety
Deal et al 1991	Capsaicin 0.025% 4 times daily vs placebo, 28 days (continued analgesic con meds allowed)	Capsaicin superior to vehicle at 2, 3, 4 weeks and throughout (p = 0.033); Day 28 VAS pain reduction 33% vs 19% for placebo (p =0.061)	Mild to moderate burning stinging pain (BSP) in 44% of treated subjects, 2 withdrew
Altman et al 1994	Capsaicin 0.025% 4 times daily vs. placebo, 12 weeks (5 target joints, knee predominant); only acetaminophen allowed	53% Reduction in VAS pain at week 12 compared to vehicle (27%) (p=0.02); improved tenderness to palpation	Mild to moderate BSP in 46% (26 of 57) of treated subjects, 2 withdrew
Schnitzer et al 1995	Capsaicin 0.25% twice daily compared to 0.025% capsaicin applied four times daily, 28 days (5 target joints, knee predominant); no analgesic con meds allowed	***Onset and extent of pain reduction is dose-dependent***; difference between groups in Pain and Responses by Day 2; Day 14 VAS pain reductions 70% vs 48% (p=0.021)	Only on Day 2 was BSP greater in 0.25% group (69% vs. 31%); average duration of BSP ~ 11d in both groups; 1 subject in 0.25% group withdrew

Objective: Develop Capsaicin Products that Disrupt the Pain Treatment Landscape

- **Improve Therapeutic Options**
  - Currently approved pain drugs have systemic exposure or dependence risks
  - Topical pain drug formulations, including OTC capsaicin, require several applications each day
  - Many chronic pain conditions are or become refractory to current therapies, such as NSAIDs
  - Newer drugs in development need to be administered by a physician, side effect concerns

- **Tactics**
  - Develop a formulation that enables the exploration of high-dose capsaicin and demonstrate in double-blinded, randomized clinical studies that the product(s):
    - are safe and well-tolerated
    - are effective with short treatment windows or few applications
    - provide long-lasting pain relief
    - are effective alone or in combination with OTC analgesics in patients with refractory OAKP

CGS-200 Product Development Timeline

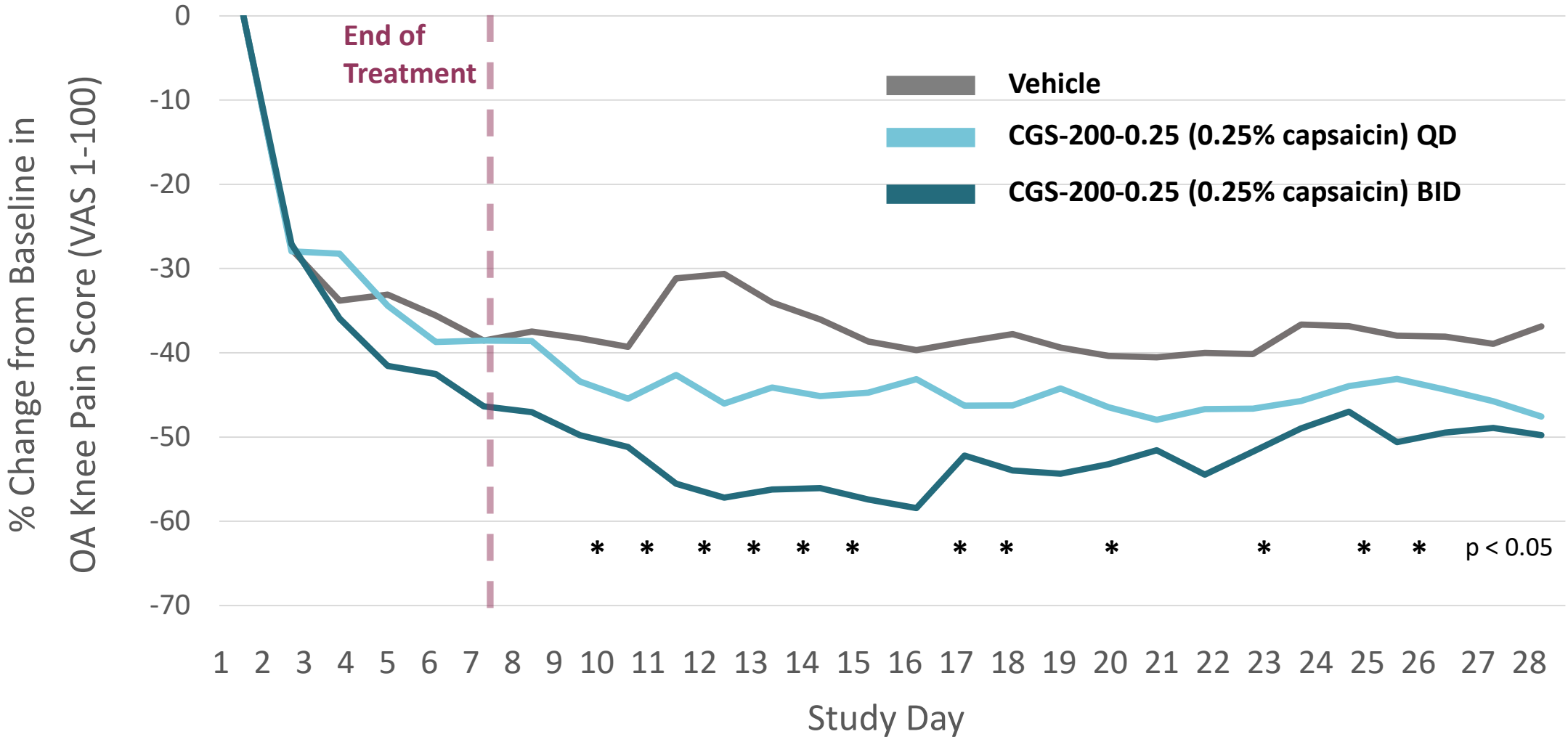


- OTC (0.25%) and prescription-strength (5%) capsaicin products developed in parallel

CGS-200 VZU00022 & VZU00025 U.S. OAKP Study Overviews

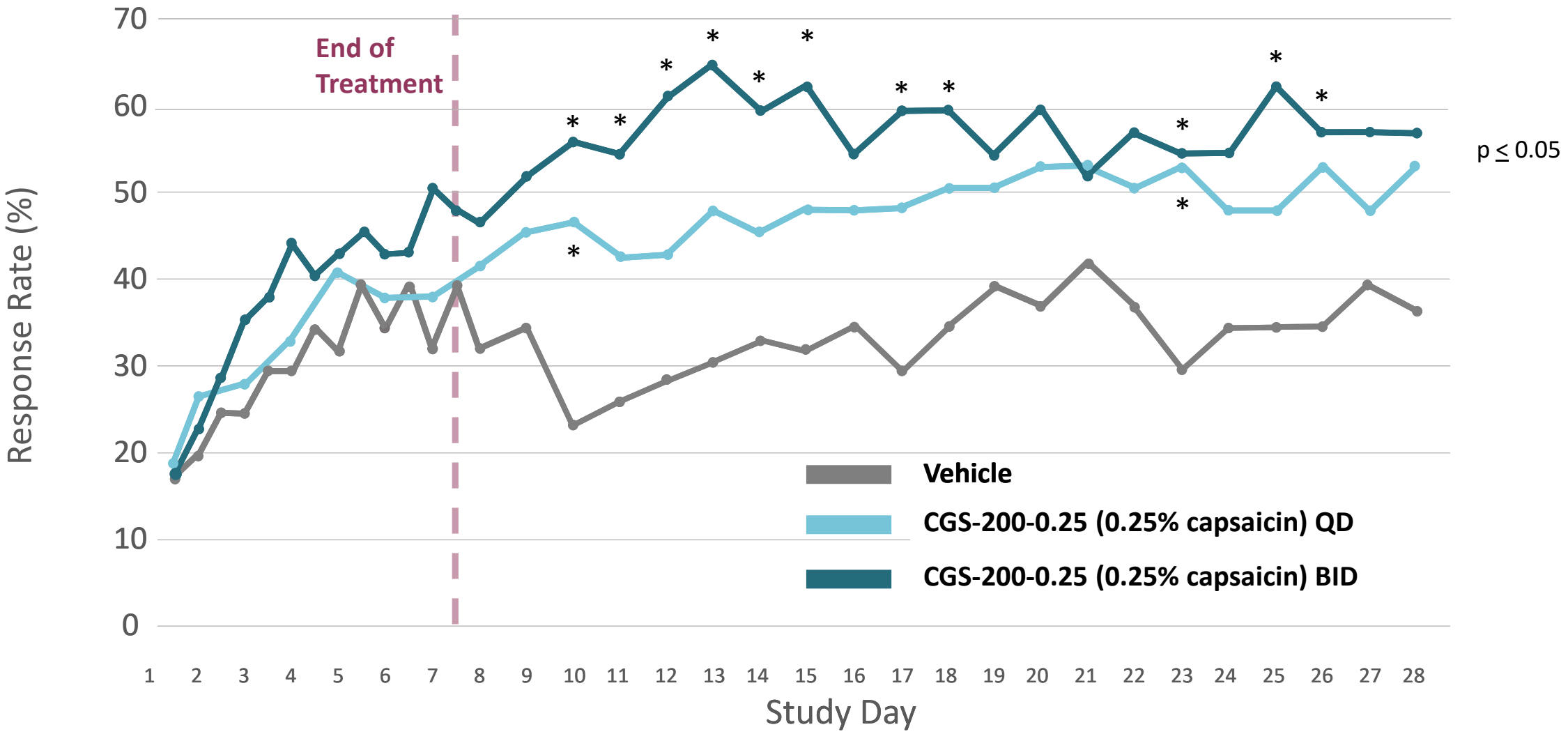
Study Number	VZU00022 (Phase 2)	VZU00025 (Phase 2)
Title	A Phase 2 Double-Blind Trial to Examine the Comparative Effects on Osteoarthritic Knee Pain of CGS-200-0.25 and CGS-200-0	A Phase 2 Double-Blind Clinical Trial to Examine the Comparative Effects on Osteoarthritic Knee Pain of CGS-200-1, CGS-200-5, and CGS-200-0
Subjects	Confirmed OA and moderate to severe baseline OAKP refractory to prior therapies	Confirmed OA and moderate to severe baseline OAKP refractory to prior therapies
Study Objectives	Assess the safety and efficacy of CGS-200 containing 0.25% capsaicin QD or BID, alone or in combination with continued oral OTC analgesics, vs. vehicle	Assess the safety and efficacy of CGS-200 containing 1 and 5 % capsaicin, alone or in combination with continued oral OTC analgesics, vs. vehicle
Enrollment	120 total; 40 per arm (vehicle = 20 per regimen)	120 total; 40 per arm
Treatment	Once- or twice-daily 60-minute application, with observation, to both knees for 7 consecutive days	Once-daily 60-minute application, with observation, to both knees for 4 consecutive days
Efficacy & Safety	Through 21 days post treatment	Through 90 days post treatment

VZU00022: Mean Reduction in Pain Score from Baseline

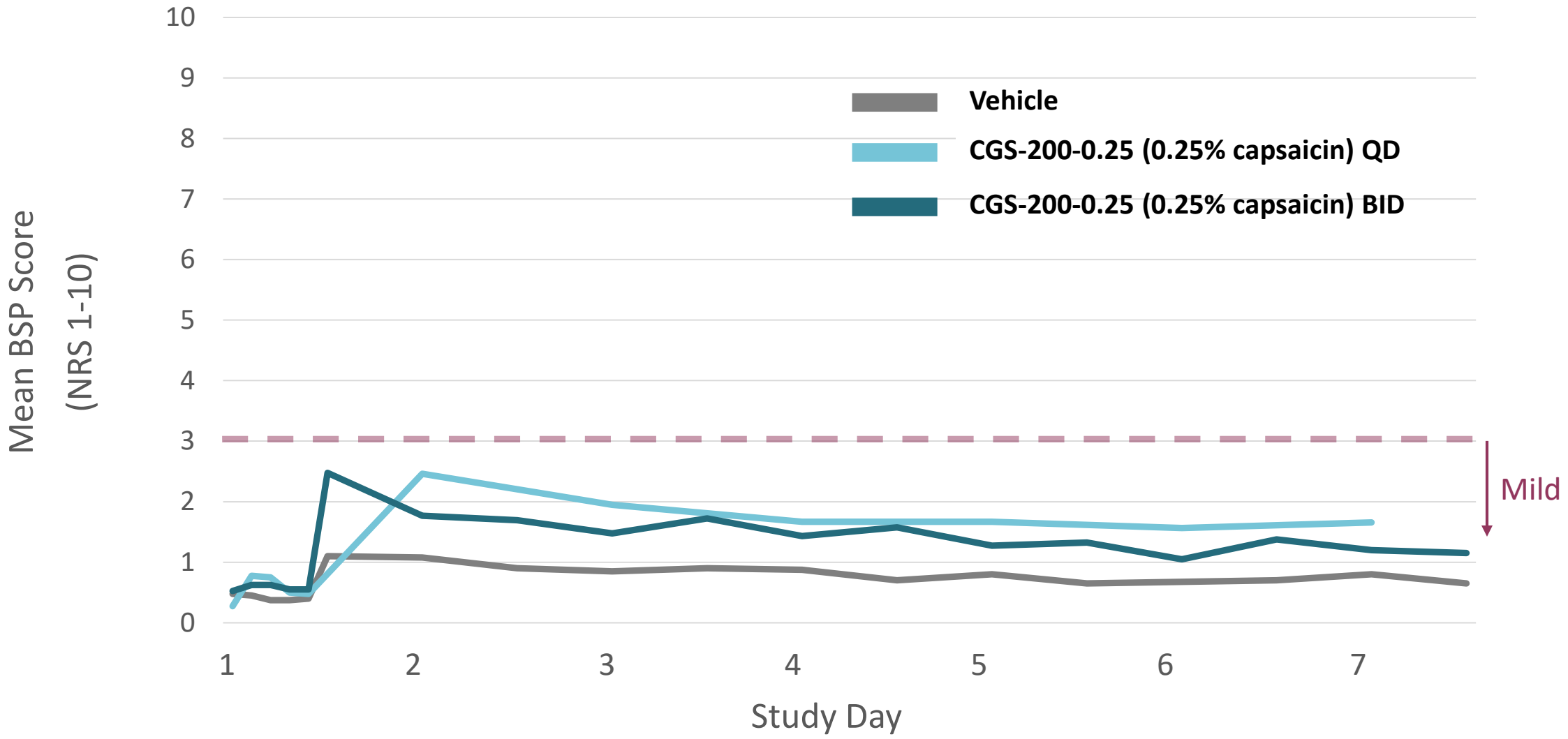


Response Rate

Proportion of Patients with ≥ 50% Decrease from Baseline VAS Pain Score



VZU00022: Mean Maximum BSP Scores (NRS 0-10)



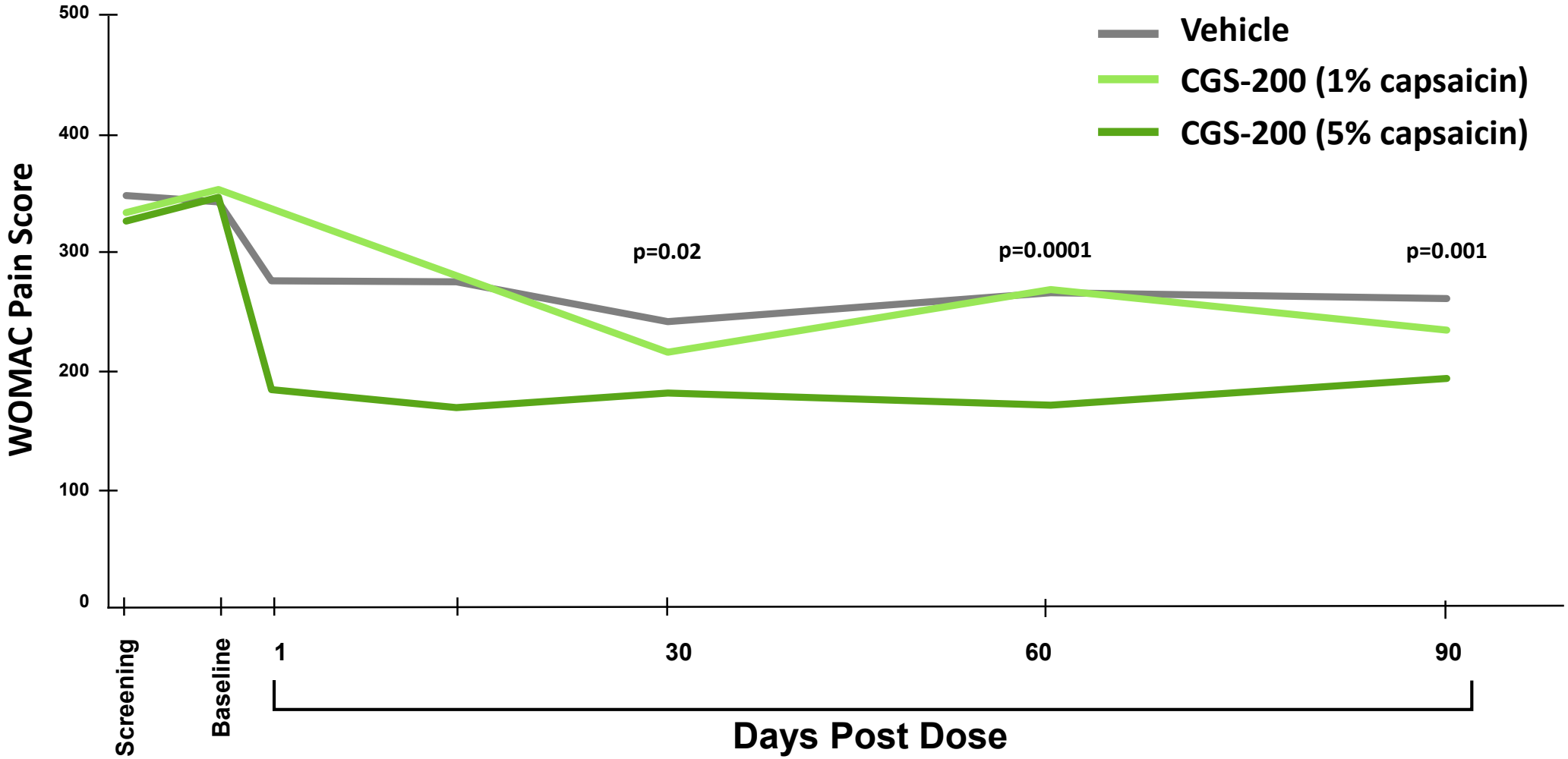
VZU00022 Study Summary

- **CGS-200 containing 0.25% capsaicin (CGS-200-0.25) was well tolerated**
  - No SAEs
  - Adverse events were primarily limited to the site of administration
  - Mild burning stinging pain upon administration; BSP decreases with re-application
    - There were no potentially drug product-related AEs aside except for initial BSP and less frequent observations of erythema or pruritus at the site of application
    - Low rates of subject discontinuation related to application site reactions (<3%)

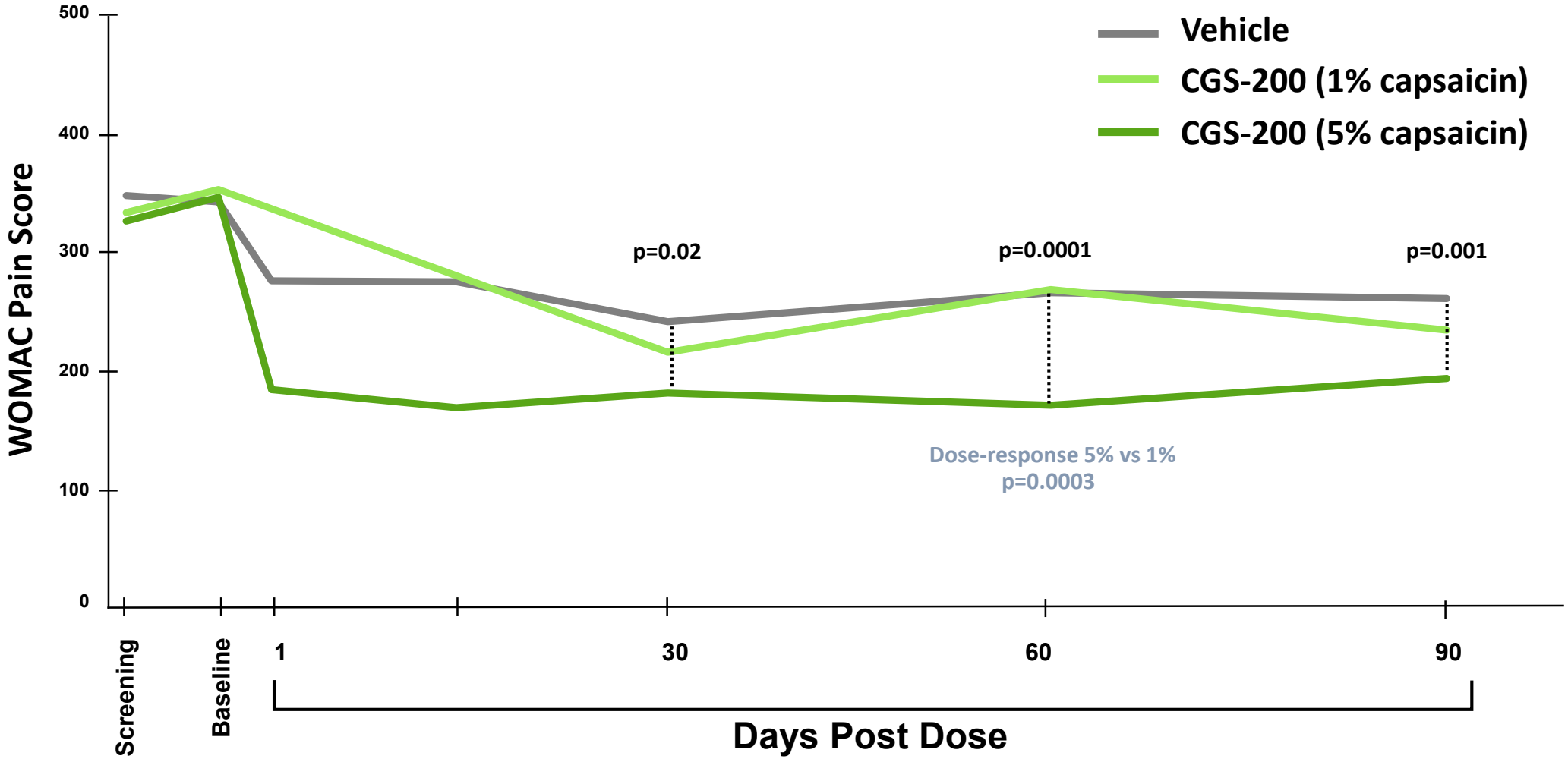
- **Long-lasting relief alone and in combination with oral OTC analgesics**
  - Durable VAS pain reductions through Day 28 (21 days post-treatment)
  - Durable clinical responses through Day 28 (21 days post treatment)

- **CGS-200-0.25 became Vizuri's first commercial OTC product, PainBloc24®**
  - Strongest OTC topical capsaicin (0.25%) analgesic available in the US

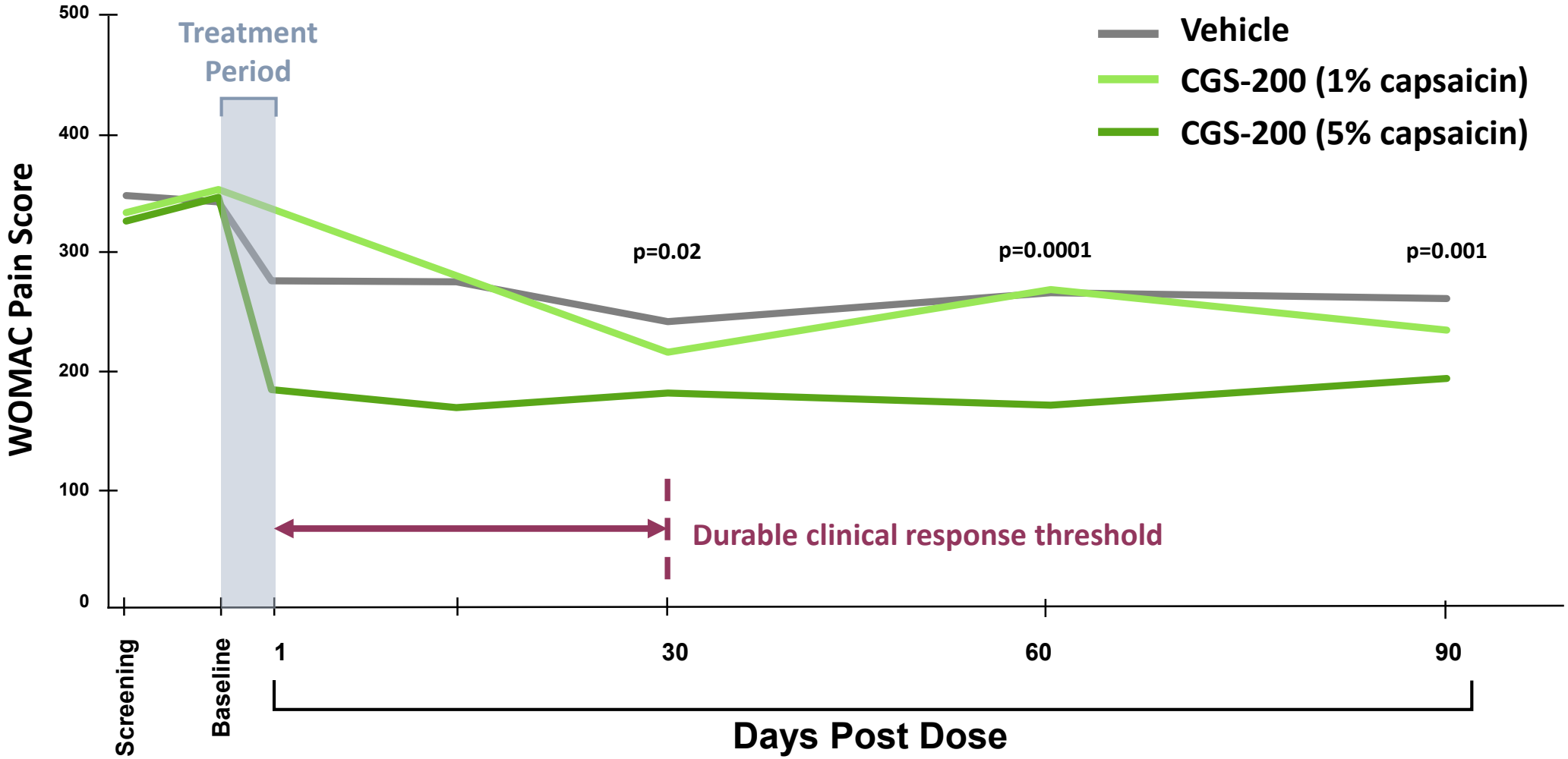
VZU00025: Change from Baseline WOMAC Pain Score



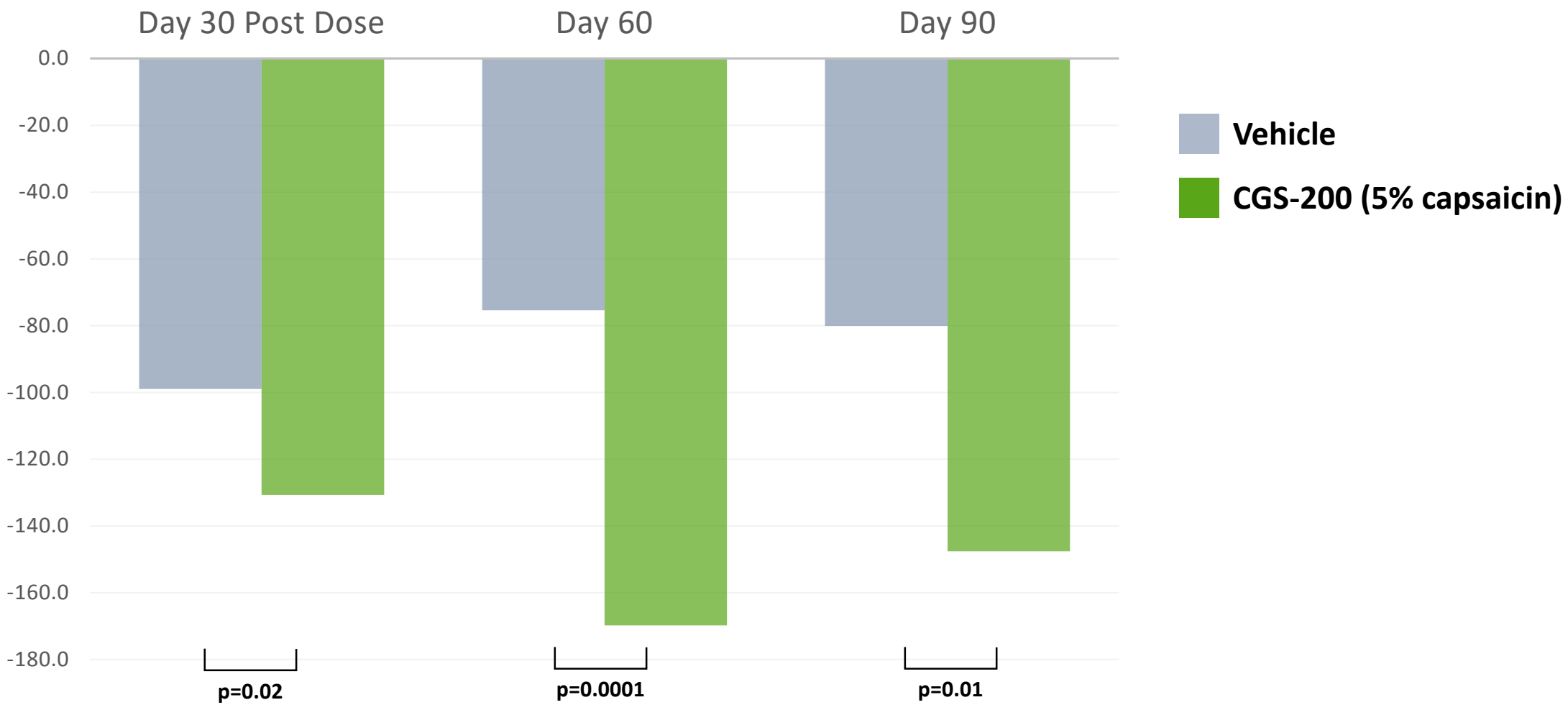
VZU00025: Change from Baseline WOMAC Pain Score



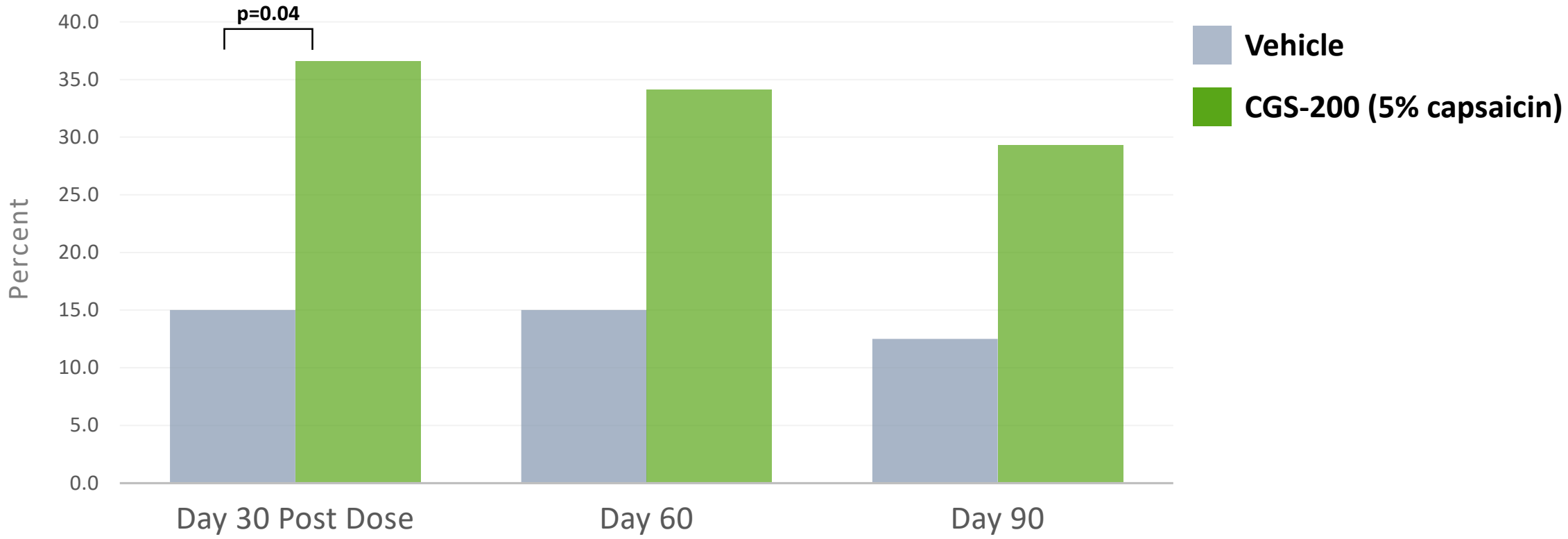
VZU00025: Change from Baseline WOMAC Pain Score



Mean Reduction in WOMAC Pain Score from Baseline

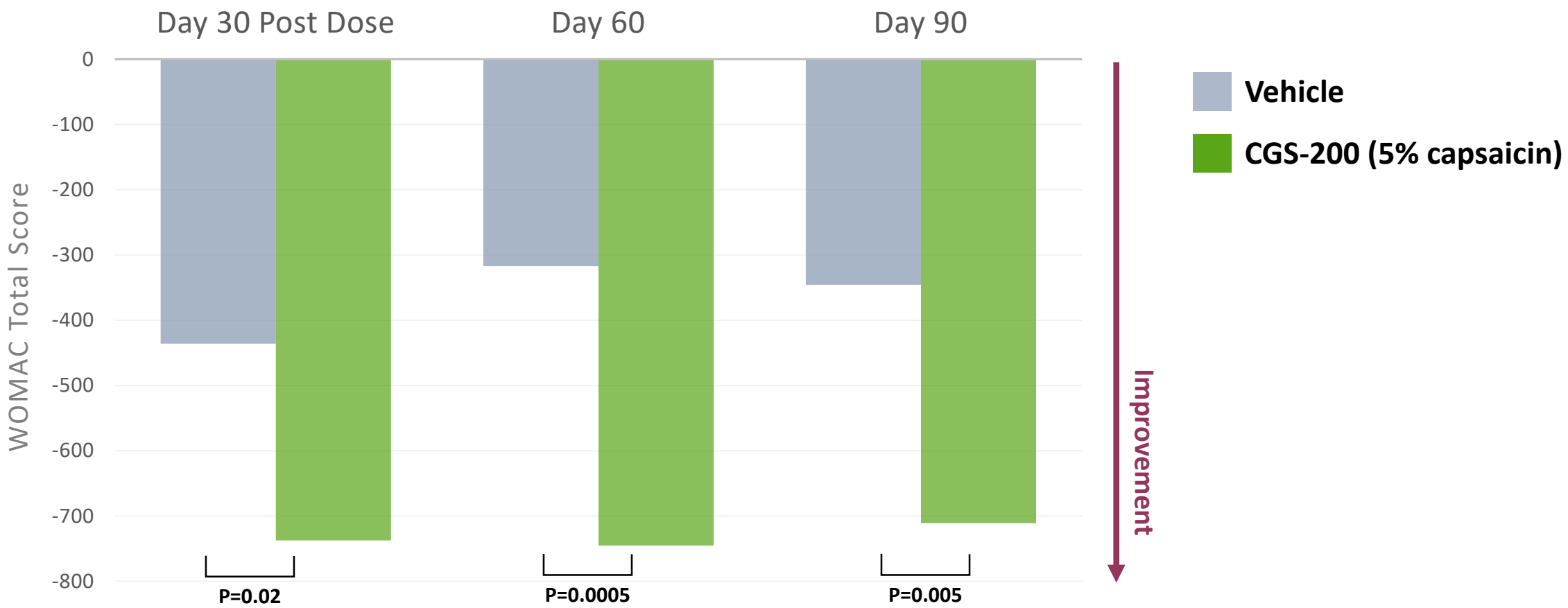


Durable Responders (Patients maintaining a ≥50% Reduction from Baseline Pain Score through Days 30, 60, and 90 Post-Dosing)

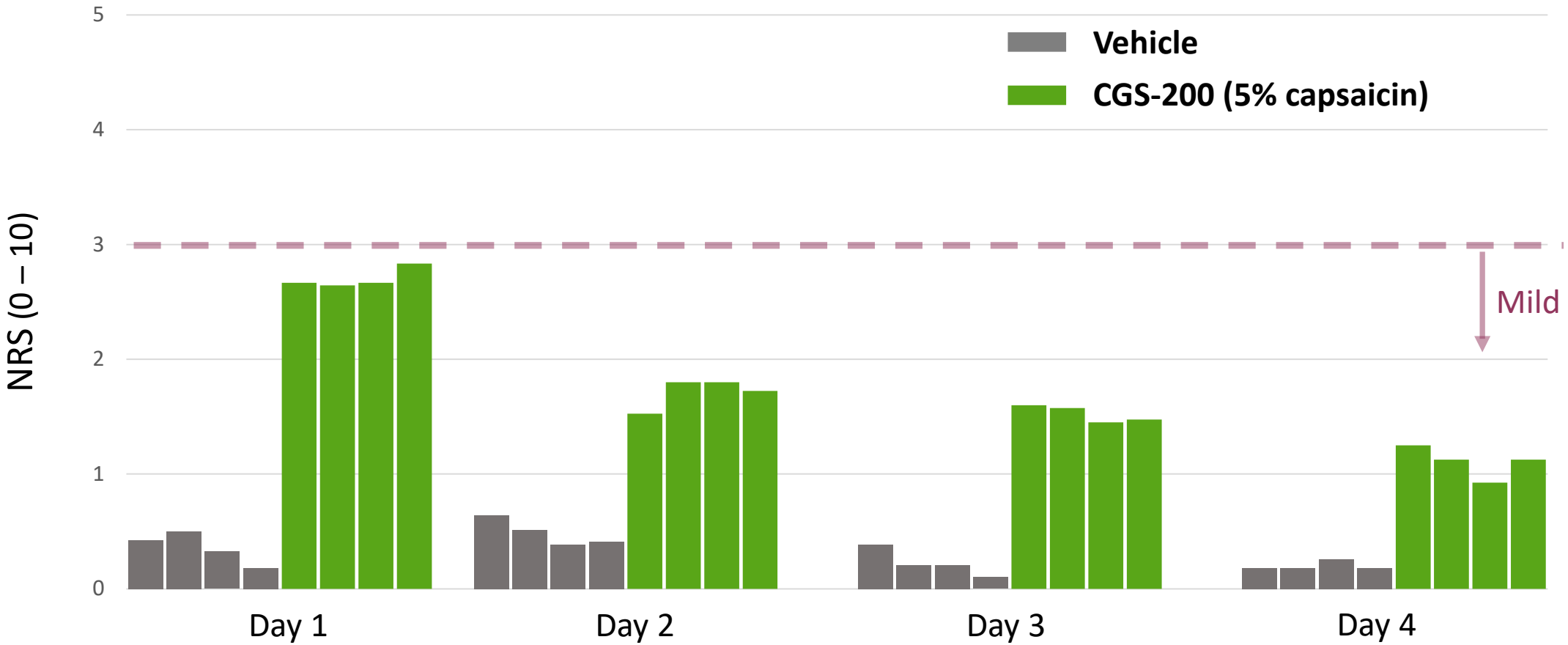


Mean Improvement in WOMAC Total Score* from Baseline

* 24 items across 3 subscales: pain (5), stiffness (2), and physical function (17)



VZU00025: CGS-200-5 is Well Tolerated



Group Mean Burning Stinging Pain at 15, 30, 60, and 90 min. following application

VZU00025 Study Summary

- **CGS-200 containing 5% capsaicin (CGS-200-5) is well tolerated**
  - No SAEs
  - Adverse events are primarily limited to the site of administration
  - Mild BSP upon administration
    - Low rates of subject discontinuation related to application site reactions (<3%)
    - BSP diminishes with subsequent re-applications

- **Four topical applications of CGS-200-5 provide long-lasting relief alone or in combination with oral OTC analgesics**
  - Improvements noted in pain and function (Total WOMAC score) through Day 90, post-dose
  - Durable clinical responses in subjects through Day 90 post-treatment
    - 36% had a ≥ 50% reduction in WOMAC pain through Day 30 post-dose, p=0.04
    - 29% had a ≥ 50% reduction in WOMAC pain through Day 90, post-dose

Technology-enabling, CGS-200 Formulation Patent Estate

	U.S.	Foreign	TOTAL
Issued	**3**	**3**	**6**
Pending	**1**	**5**	**6**

CGS-200 is a powerful combination of inert ingredients designed to mitigate BSP:

- Ethoxydiglycol methyl ether
- Ethyl alcohol
- Hyaluronic acid mixture
- Polysorbate 80
- Propylene glycol
- Water

CGS-200-5 Program Plans

- **Planning is underway for OAKP registration studies (EOP2 FDA meeting mid-2020)**
  - The initial indication will be management of pain due to osteoarthritis of the knee
- **A pilot Phase 2 study in pain due to OA of the hand is planned for early 2020**
  - Planning to evaluate functional improvements as well as pain
- **Company to present at American College of Rheumatology Annual Meeting in November 2019**
  - Presentation will provide detailed results from the VZU00025 OAKP study

Acknowledgements

CGS-200 Advisory Board Members

Marc Hochberg, MD, MPH, MACP, MACR

Anne-Marie Malfait, MD, PhD

Neil Singla, MD

The VZU00022 and VZU000025 Patients and Investigators

Vizuri Employees and Consultants, Present and Past

The Peterson Family