Capsaicin the Near Perfect Modulator of TRPV1, the Ideal Osteoarthritis (OA) Pain Target

February 9th 2021

PROPELLA

Introduction

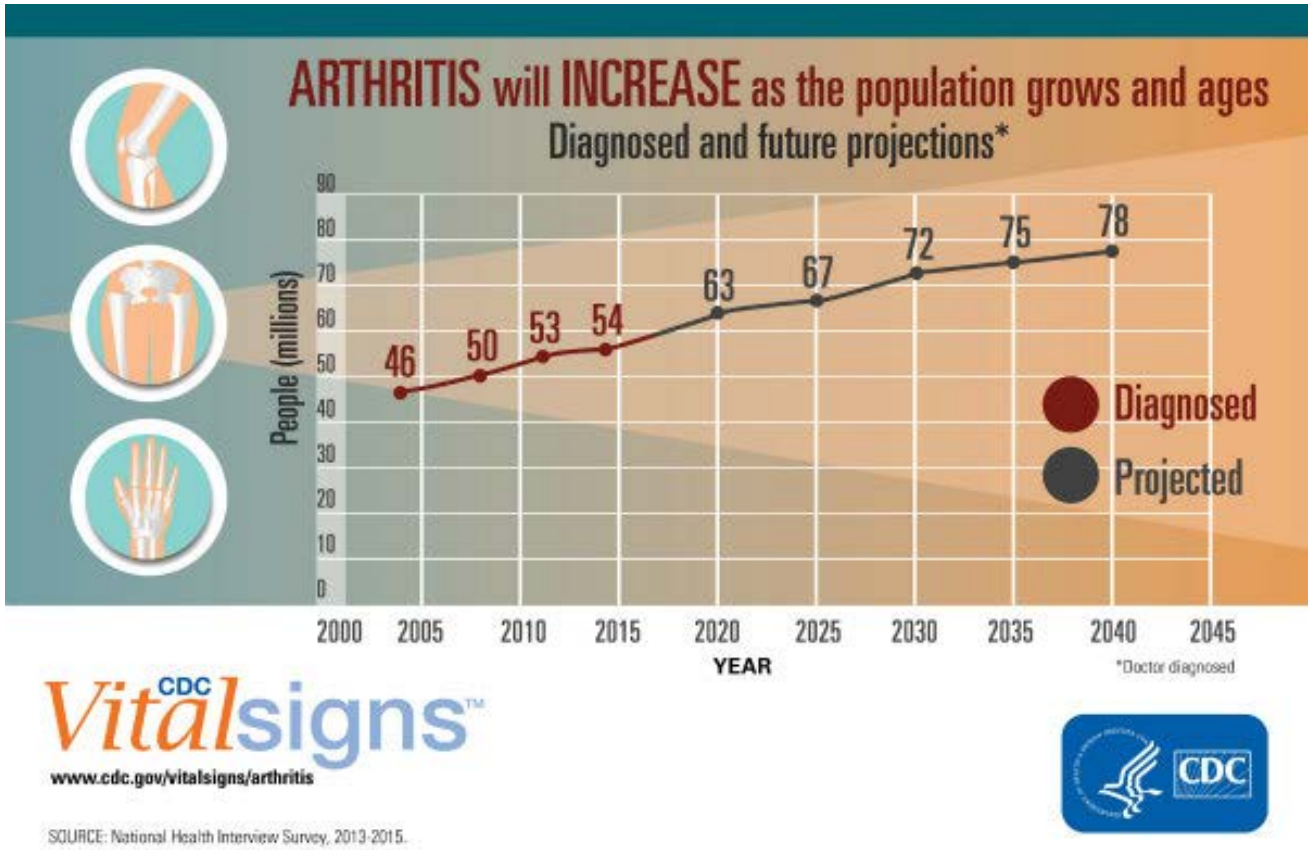
PROPELLA

bright ideas made brilliant

- Privately-held Propella is a development-stage company dedicated to bringing to market best-in-class drugs that utilize an active ingredient with a known mechanism of action.
- Our lead product candidate, topical CGS-200-5, is being developed for the management of knee pain due to osteoarthritis and it is now Phase 3 ready, having successfully completed a predictive Phase 2 study.

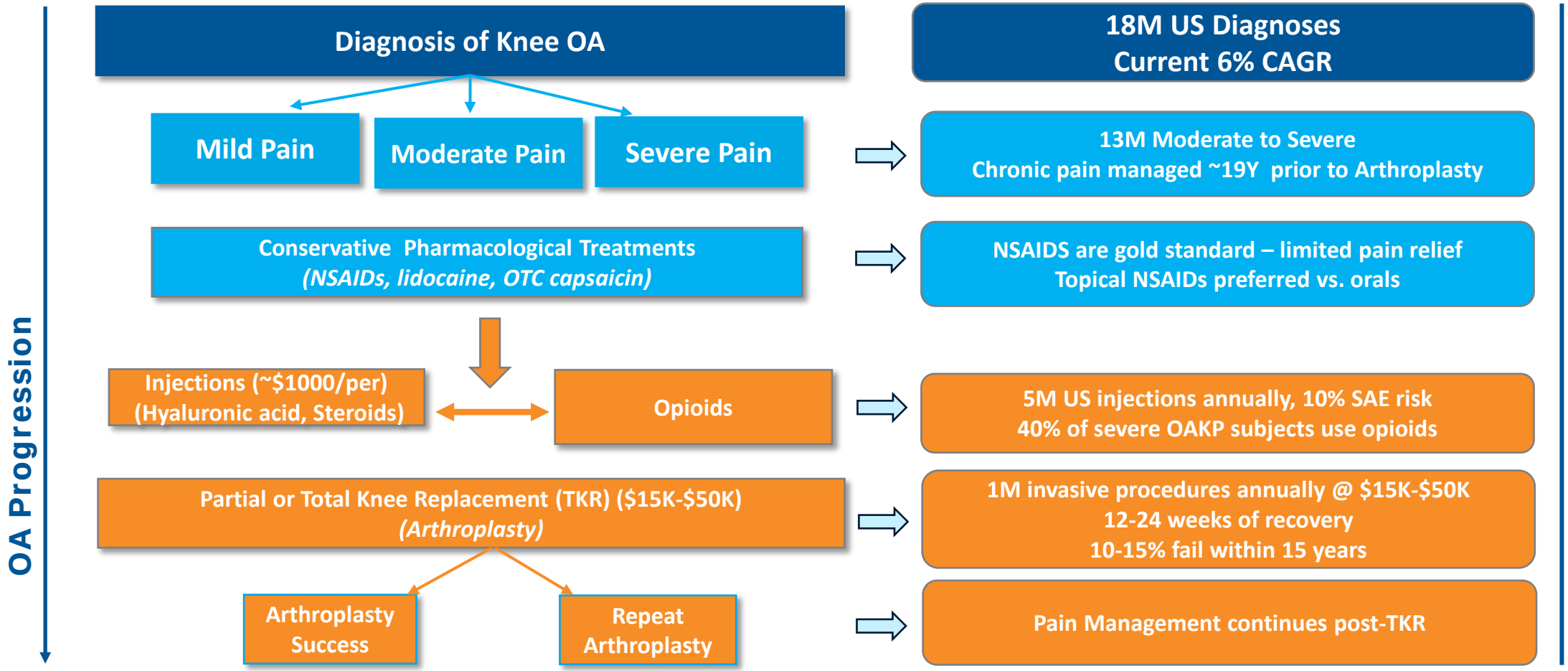
Tim Warneke, Vice President of Clinical Operations at Propella Therapeutics, has more than 30 years of pharmaceutical development experience in clinical operations. Prior to Propella Therapeutics, Tim led the clinical development team at BioDelivery Sciences International that obtained FDA approval of Belbuca® for the management of chronic pain requiring opioids.

OA Pain: A High Unmet Medical Need



- 23% of the US population suffers with arthritis
- OA is the most common form of arthritis
- An estimated 18 million patients experience symptomatic OA of the knee
- Rising rate of obesity in an aging population will be putting greater pressure on health services to treat OA knee pain (OAKP) in the future

Deferring Surgery and Managing OAKP is the Treatment Goal

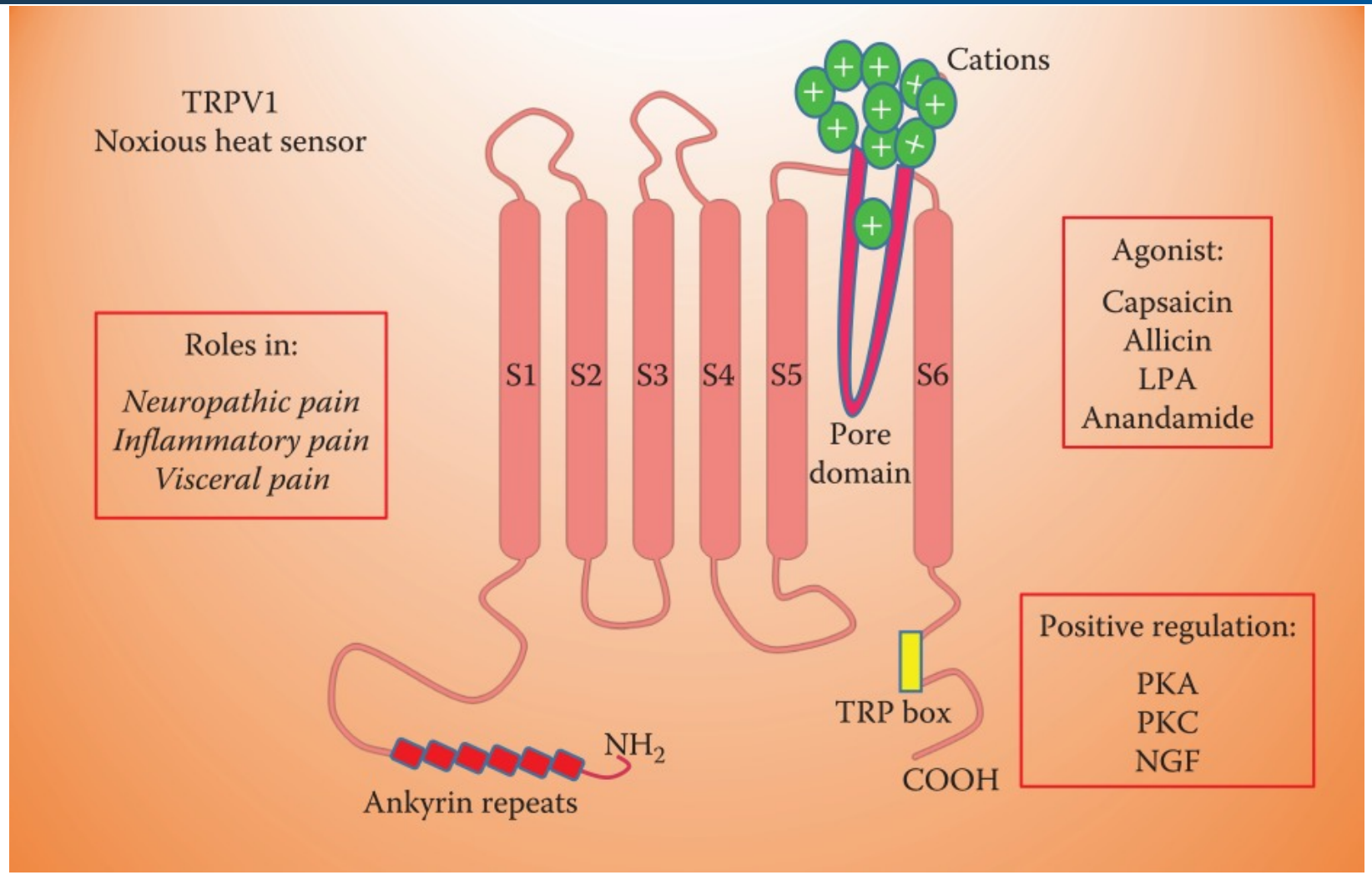


What is Missing from the OAKP Treatment Landscape?

- **A front-line pharmacological treatment that delays more aggressive therapy, particularly TKR**
  - An **effective** analgesic
  - Durable relief
  - Safe and well tolerated, ideally non-systemic
  - Offers patient convenience

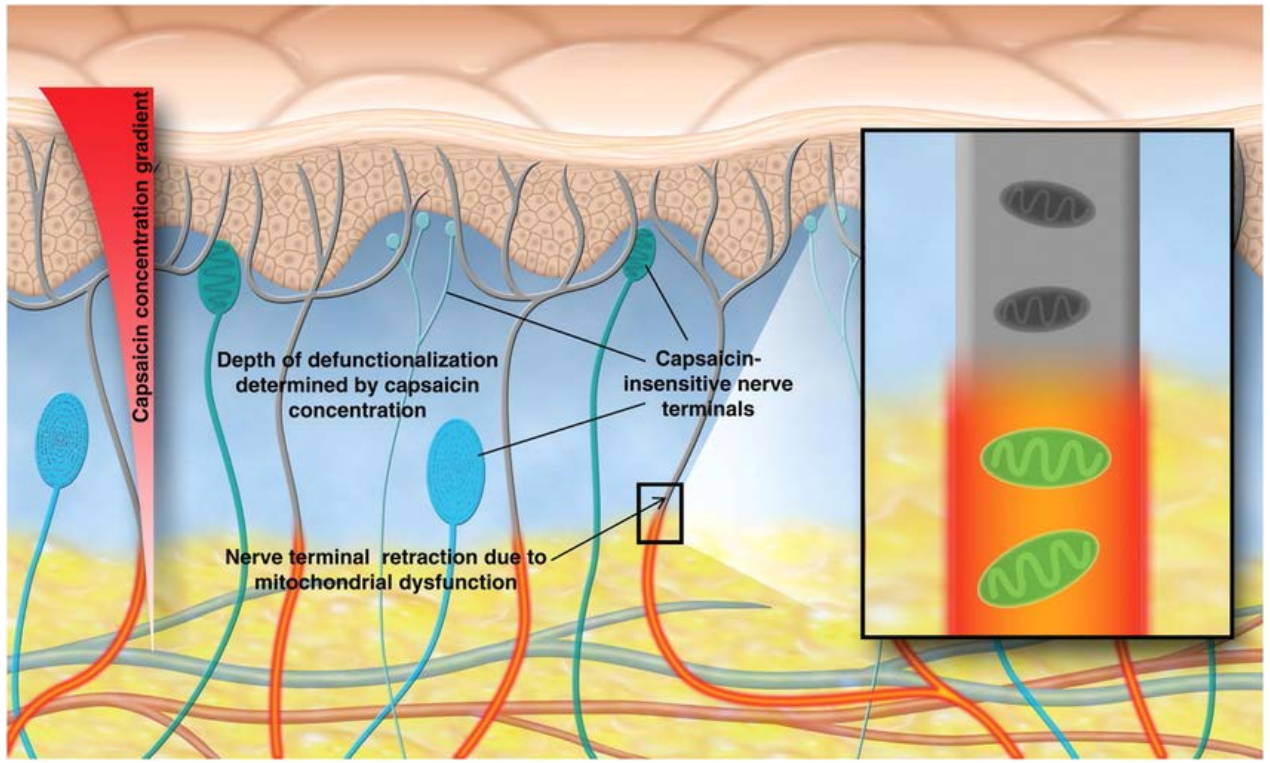
- **Capsaicin, the near perfect modulator of TRPV1, may be the ideal OAKP disrupter**

TRPV1 Structure, Regulators, and Role in Pain Transmission



González-Ramírez et al.
TRP Channels and Pain;
Emir TLR, editor. Neurobiology of TRP Channels. 2017. Chapter 8.

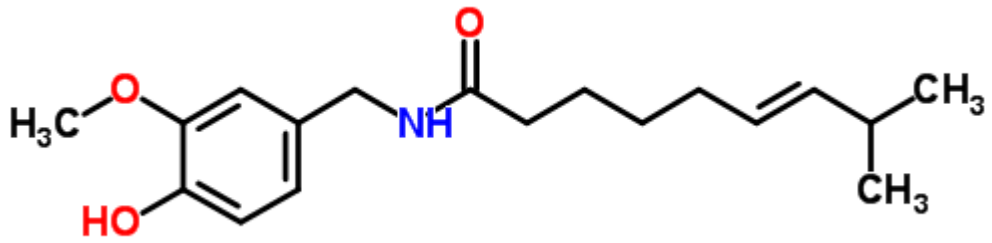
Mechanism of TRPV1 Nociceptor Desensitization by Capsaicin



Bley, K. https://www.researchgate.net/figure/Fig4-The-site-of-action-of-topical-capsaicin-is-in-the-skin-and-pain-relief-is-not_fig1_51581406

- Capsaicin is a highly selective agonist (EC50 = 0.2 µM) of the TRPV1 receptor that is highly expressed in myelinated A_{delta}-fibers and unmyelinated C-fibers of afferent sensory nerves
- Repeat exposure to capsaicin promotes an analgesic response through desensitization of these sensory neurons, in part due to the physical shortening of these peripheral nerve fibers
- The time for nerve fiber regrowth correlates with the duration of efficacy of highly concentrated topical capsaicin formulations

Capsaicin Pungency



- The substance that gives chili peppers their pungency when ingested or applied topically is capsaicin, 8-methyl-N-vanillyl-6-nonenamide (structure above)

- Capsaicin, mostly from natural sources, is used as an analgesic in topical creams, nasal sprays, and dermal patch pain products

- On a weight basis, pure synthetic capsaicin is a stronger TRPV1 agonist than capsaicin from natural sources (Scoville scale)

Chili Pepper	Scoville Rating
Pure Capsaicin	15.000.000
Nordihydrocapsaicin	9.100.000
US Pepper Spray	2.000.000-5.500.000
Naga Jolokia	855.000-1.041.427
Red Savina Habenero	350.0000-577.000
Habanero Chili, Scotch Bonnet	100.000-350.000
Jamaican Hot Pepper, Rocoto	100.000-200.000
Thai Pepper, Malagueta Pepper Chiltepin Pepper, Pequin Pepper	50.000-100.000
Cayenne Pepper, Ají Pepper Tabasco Pepper	30.000-50.000
Serrano Pepper	10.000-23.000
Wax Pepper	5.000-10.000
Jalapeño Pepper	2.500-8.000
Rocotillo Pepper	1.500-2.500
Poblano Pepper	1.000-1.500
Anaheim Pepper	500-2.5000
Pimento	100-500
Bell Pepper	0

The Analgesic Benefit of Topical Capsaicin is Well-established

- Capsaicin has been recognized by the FDA In 1973 FDA recognized that topical capsaicin was effective and safe - to a point!
- Due to BSP, FDA limited capsaicin concentrations in OTC topical analgesics to 0.25% and applications to not more than 3 to 4 times daily
- In deference to BSP concerns, few marketed products contain 0.25% capsaicin

<u>Typical OTC product concentrations:</u>

- 0.025%
- 0.035%
- 0.075%
- 0.1%

OTC Capsaicin Pain Efficacy Established in RCTs

Author/Year	Study Design	Duration	Population	Treatments	Pain at Entry	Results
Deal, et al. (1991)[1]	Multi-center, randomized, double-blind, placebo-controlled study of 0.025%	4 weeks	OA and RA knee pain	0.025% QID (N=52) or placebo QID (N=49)	Moderate to severe	Pain reduction at Week 4 (*p*= .033)
Altman, et al. (1994)[2]	Multi-center, randomized, double-blind, placebo-controlled study of 0.025%	12 weeks	OA joint pain	0.025% QID (N=57) or placebo QID (N=56)	Moderate	Pain reduction at Week 12 (*p*= .02)
Schnitzer, et al. (1995)[3]	Multi-center, randomized, single-blind, comparator study of 0.25% vs 0.025%	28 days	OA joint pain	0.25% BID (N=32) or 0.025% QID (N=32)	Moderate to severe	Day 2 (*p*= 0.0009) Day 14 (*p*=0.021) Day 28 (*p*= 0.278)

[1] Dean C. L., et al., Clinical Therapeutics Vol 13, No 3, 1991
[2] Altman R.D., et al., Capsaicin Cream 0.025% as Monotherapy for Osteoarthritis: A Double-Blind Study, Seminars in Arthritis and Rheumatism, Vol 23. No 6, Sup 3, 1994
[3] Schnitzer T. J., et. al., High Strength Capsaicin Cream for Osteoarthritis Pain: Rapid Onset of Action and Improved Efficacy with Twice Daily Dosing, Journal of Clinical Rheumatology, Vol 1. No 5, October 1995

OTC Product Pain Relief Was Recognized As Inadequate

- **"Topical capsaicin cream is a safe pain-relieving medication that was not associated with systemic side effects. It is suggested that topical capsaicin cream be considered first line therapy for OA."**

  Altman R.D, et al., Capsaicin Cream 0.025% as Monotherapy for Osteoarthritis: A Double-Blind Study, Seminars in Arthritis and Rheumatism, Vol 23. No 6, Sup pi 3, 1994: pp 25-33

- **"It may be necessary to apply the drug (low concentration capsaicin) at least three or four times daily to produce or maintain pain relief."**

  Dean C. L., et al., Clinical Therapeutics Vol 13, No 3, 1991

- **"With… a high strength capsaicin preparation, the drawbacks associated with a less than optimal dosing regimen and a slower onset of action have been eliminated."**

  Schnitzer T. J., et. al., High Strength Capsaicin Cream for Osteoarthritis Pain: Rapid Onset of Action and Improved Efficacy with Twice Daily Dosing, Journal of Clinical Rheumatology, Vol 1. No 5, October 1995

2012 American College of Rheumatology Treatment Guidelines - *Conditionally recommended* ***against*** *topical capsaicin for the treatment of OAKP* due to reports of limited pain relief

TRPV-1 Agonists for the Management of Pain

All TRPV-1 agonists cause burning-sting pain (BSP), but…not all TRPV-1 agonists are capsaicin

- With the discovery of TRPV1 may pharmaceutical companies initiated ‘vanilloid receptor’ programs, with a goal of finding more potent TRVP1 agonists than capsaicin and which did not cause BSP
- These synthetic programs failed due to TRPV1 biology - it is not possible to decouple receptor stimulation and BSP
- Some have turned to new natural sources for TRPV1 agonists
- Sorrento Therapeutics is developing resiniferitoxin (RTX), produced by the Moroccan mound plant (right) and with 500x greater affinity for TRPV1 than capsaicin, as an AI injection for OA pain

Renewed Interest in Capsaicin Prescription Pain Products

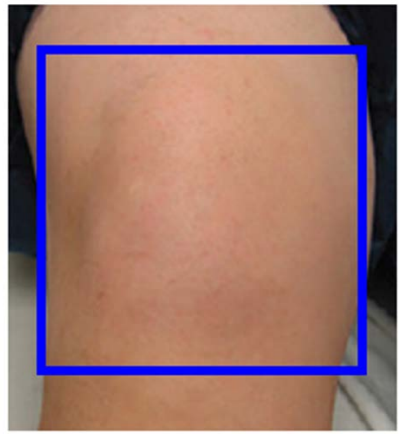
- **QUTENZA 8% capsaicin patch** – **A**pproved for the treatment of postherpetic neuralgia (PHN)
  - Recently also approved for treatment of diabetic peripheral neuropathy (DPN)
- **Centrexion Therapeutics** – Intra-articular capsaicin injection for OAKP
  - CNTX-4975: Phase 3 studies recently completed
- **Concentric Analgesics** – Wound bed infiltration of a capsaicin pro-drug for acute post-surgical pain
  - CA-008: Phase 2 completed

A Topical Approach to the Capsaicin Conundrum

- **A Phase 2 Double-Blind Clinical Trial to Examine the Comparative Effects on Osteoarthritic Knee Pain of CGS-200-1 (1% Capsaicin Topical Liquid), CGS-200-5 (5% Capsaicin Topical Liquid), and CGS-200-0 (Vehicle, No Capsaicin)**
  - CGS-200-5 is up to 50 times stronger than OTC products; proprietary formulation minimizes the typical topical capsaicin effects and enhances penetration
  - Designed to be applied by the patient; no pre-treatment with an analgesic, no special cleaning gels

CGS-200-5 Applicator and Administration to the Knee

- **CGS-200-5 Topical Liquid is supplied in single-use rollerball applicators with precisely enough product to cover a 10X10 cm^2 area on top of the knee**
  - Applied by multiple single passes of the applicator across the target area
  - As the drug is applied to the skin it leaves a wet streak that allows the subject to visualize where drug was applied
  - The product is intended for patient self-administration



Phase 2 OAKP Study (VZU00025) Design Overview

- **A Phase 2 Double-Blind Clinical Trial to Examine the Comparative Effects on Osteoarthritic Knee Pain of CGS-200-1 (1% Capsaicin Topical Liquid), CGS-200-5 (5% Capsaicin Topical Liquid), and CGS-200-0 (Vehicle, No Capsaicin)**
  - 6 US clinical research sites

- **Primary Efficacy Endpoint**
  - The extent of reduction in WOMAC pain score from baseline in the “study knee” at Study Day 35 compared to placebo (vehicle)

- **Secondary Endpoints**
  - Efficacy – WOMAC pain, stiffness, function and total scores versus baseline at Days 5, 19, 35, 64 & 94
  - Safety – AEs through Day 94, evaluation of concomitant pain medication use
  - Tolerability – Subject reports of burning, stinging pain (BSP) and pruritis; Investigator observations of edema, scaling, erythema

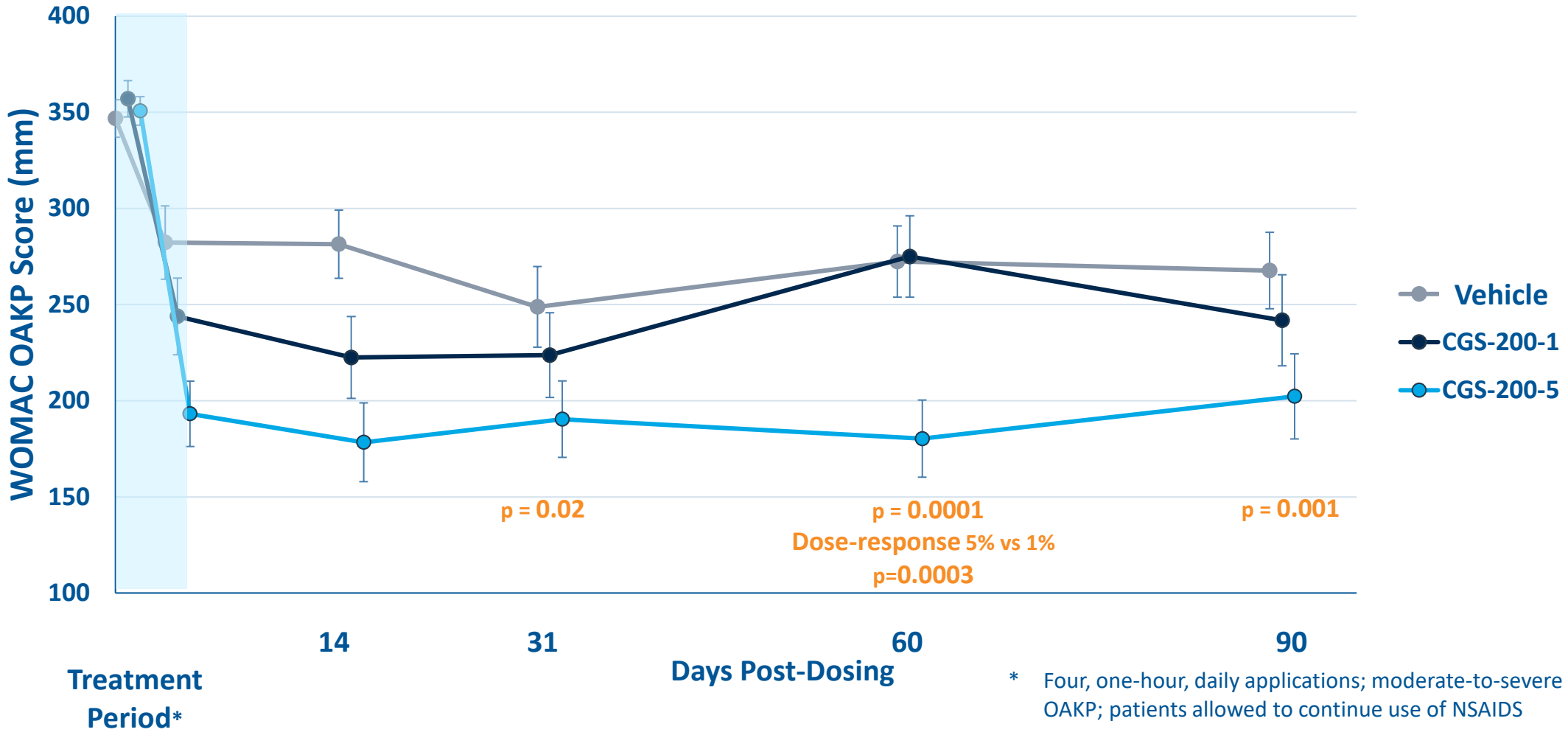
WOMAC Questionnaire Overview

- **The WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index™ is a validated questionnaire that measures three subscales – pain (5 questions), stiffness (2 questions) and physical function (17 questions)**
  - Commonly used and accepted by regulatory authorities
  - Subject self-administered
  - Responses can be collected using a 100mm VAS, 11-point NRS or 5-point Likert scale
  - In VZU00025 subjects used the 100mm VAS to complete their WOMAC Questionnaires
  - WOMAC Total score (0 – 2400) considers the totality of all 24 questions

Phase 2 OAKP Study (VZU00025) Design Overview

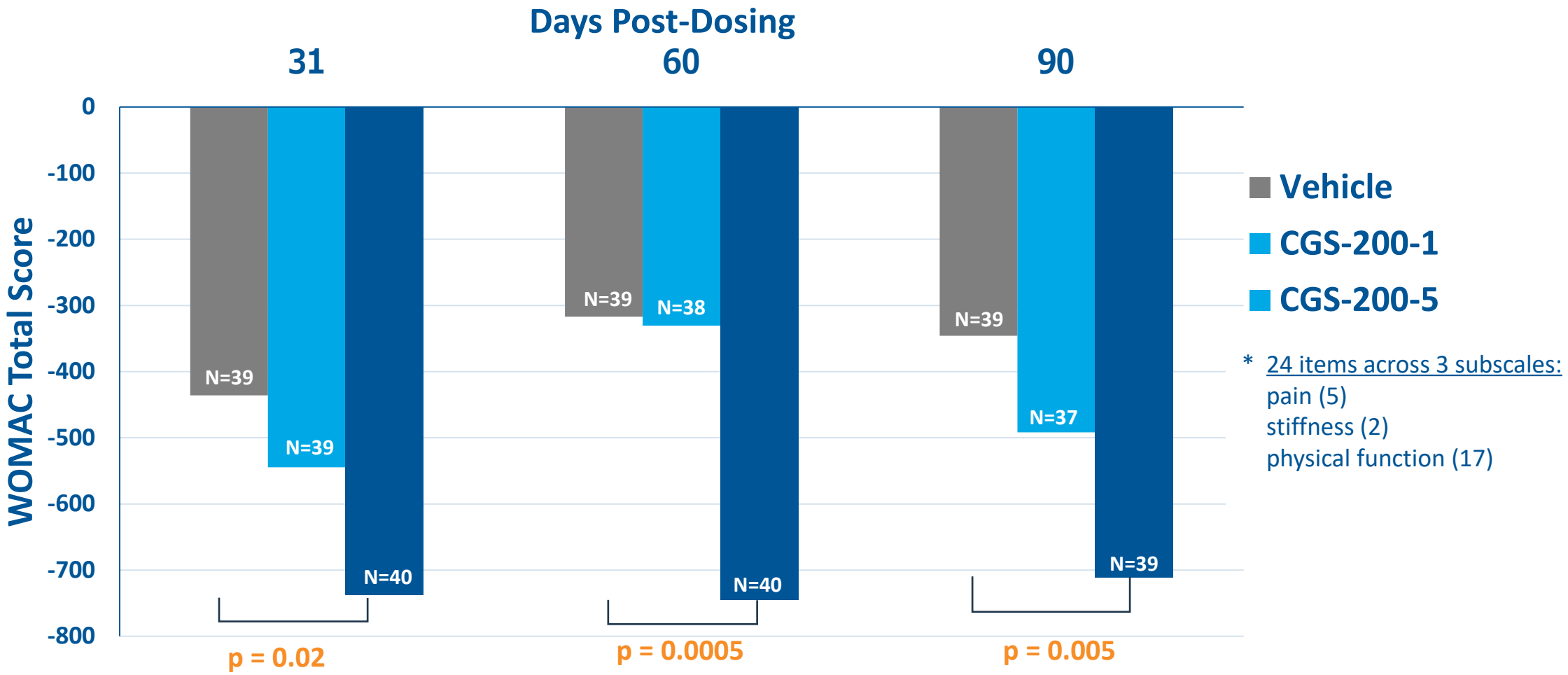
- **Subjects (n=122)**
  - CGS-200-0 (n=40), CGS-200-1 (n=40), and CGS-200-5 (n=42)
- **Treatments**
  - Once-daily, 60-min application to both knees on 4 consecutive days (Study Days 1-4)
  - Applied by the subject and washed-off after 60 minutes with cool water and soap
- **Tolerability Assessments**
  - Site application burning-stinging pain, edema, scaling, erythema, and pruritis were assessed on Study Days 1-4 at pre-dose, 15, 30, 60 and 90 minutes and Study Day 5
- **Follow-up**
  - Efficacy and safety assessments on Study Days 5, 19, 35, 64 and 94

Substantial Reductions in Mean WOMAC Pain Scores from Baseline



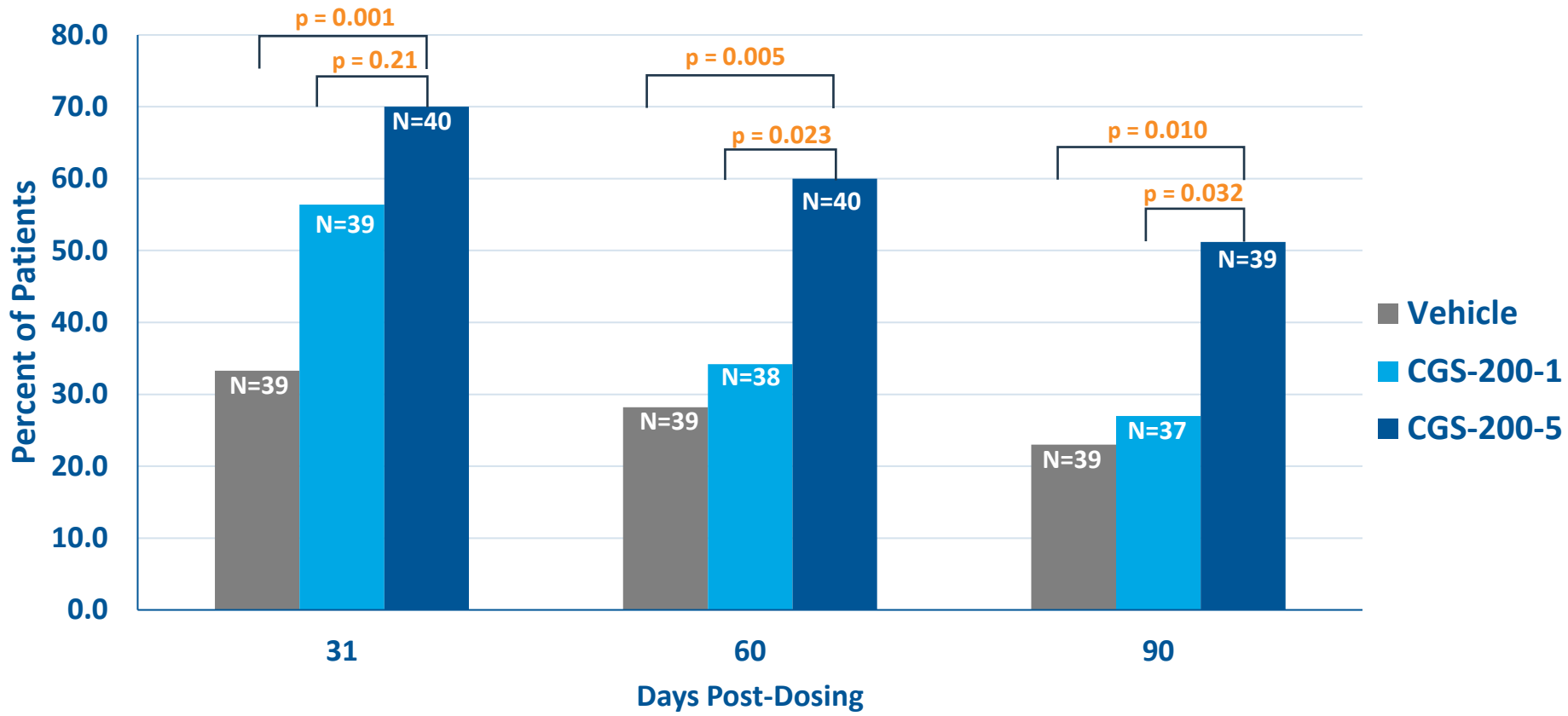
* Four, one-hour, daily applications; moderate-to-severe OAKP; patients allowed to continue use of NSAIDS

Impressive Reductions in Mean WOMAC Total Score* from Baseline

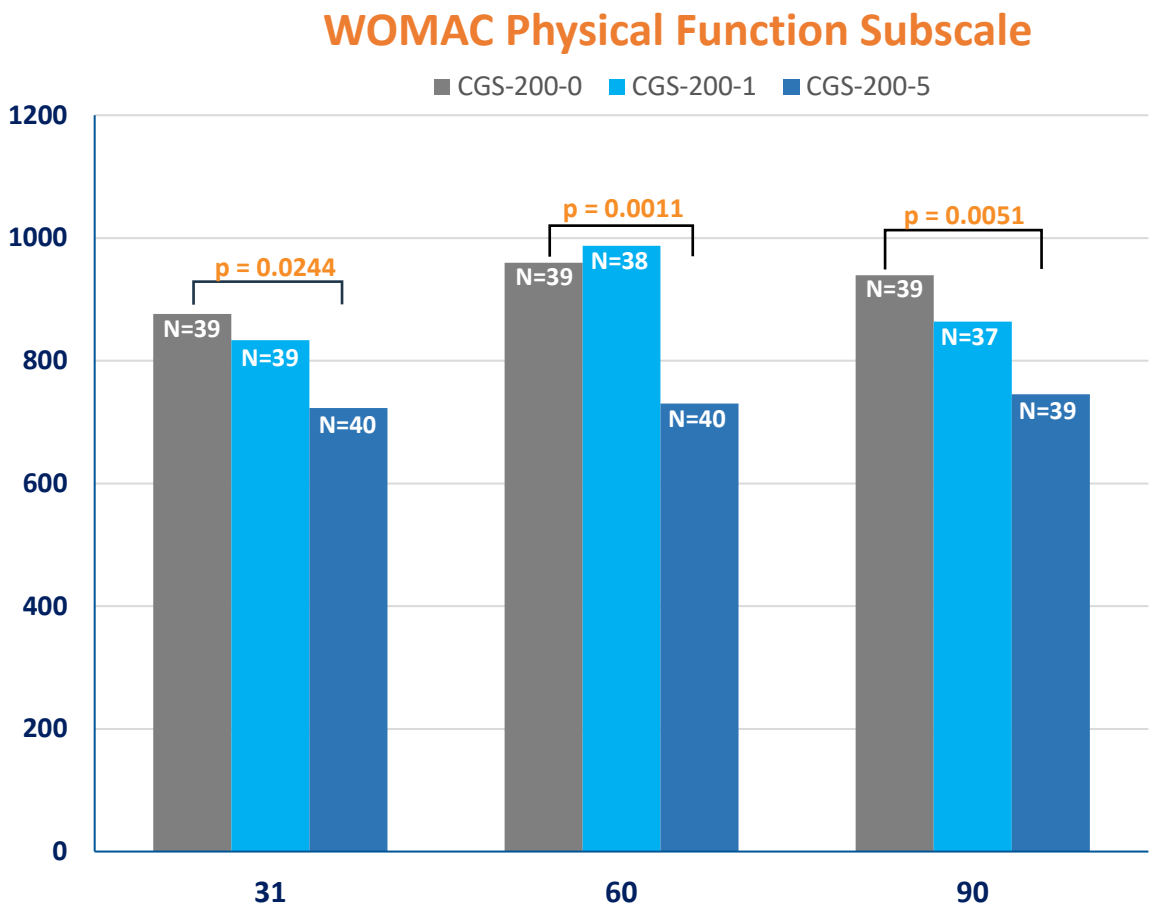


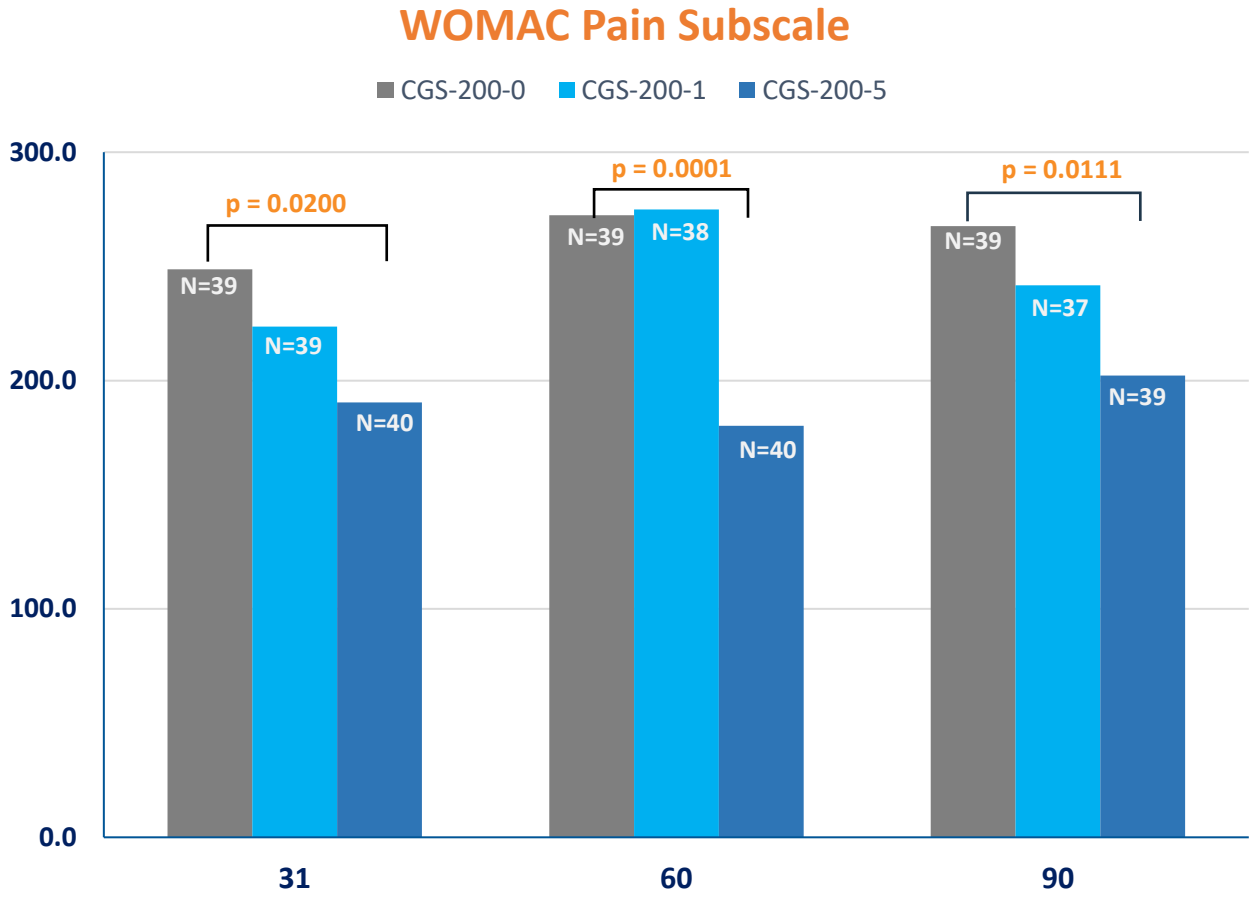
* 24 items across 3 subscales:
pain (5)
stiffness (2)
physical function (17)

A High Proportion of Durable Responses
% of patients maintaining ≥30% reduction from baseline pain score



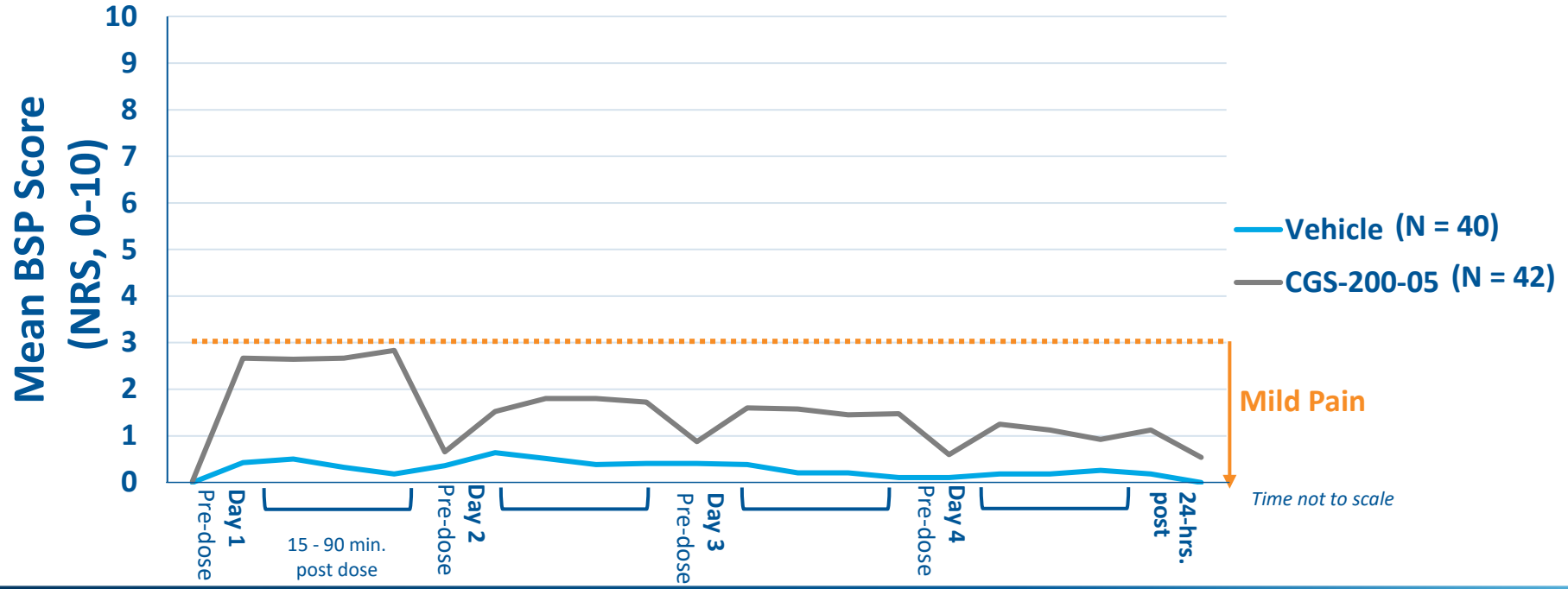
WOMAC Physical Function and Pain Results





Excellent Phase 2 Tolerability Results

- CGS-200-5 was very well tolerated in Phase 2 due to proprietary formulation designed to mitigate the historical poor tolerability of capsaicin
- 'Burning or Stinging Pain' (BSP) was most frequent tolerability complaint; diminished with each treatment, was mild and self-resolving (note: BSP score $\leq$ 3 is "minimal")



The ‘Capsaicin Conundrum’ Appears to Have a Solution!

- CGS-200-5 is the ‘Solution’ – 50 times stronger than OTC products; 4 once-daily applications provide 90 days of pain relief and improved physical function in OAKP with minimal tolerability issues
- CGS-200-5 addresses the inadequate pain relief and inconvenient dosing regimens provided by OTC strength products
- Following presentation of CGS-200-5 Phase 2 OAKP results, the American College of Rheumatology updated its OAKP Treatment Guideline to a ***conditional recommendation for topical capsaicin use*** “due to the availability of new clinical data”, reversing the 2012 recommendation against capsaicin use

CGS-200-5 Potential and Partnerships

Potential Indications for Future Development

- OA of joints amenable to topical treatment other than OA of the knee (e.g., hand, elbow, ankle)
- Diabetic peripheral neuropathy (DPN)
- Chronic lower back pain (CLBP)
- Post-surgical pain

We value and wish to hear from parties who share our motivation to accelerate the development of CGS-200-5 pain indications of high unmet need

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