

Sustained Clinical Effects After a Single Intraarticular Injection of PCRX-201 for Moderate-to-Severe Osteoarthritis of the Knee

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PCRX-201 IS NOT FDA APPROVED FOR USE

Dr Stanley Cohen

- Board-certified rheumatologist with Rheumatology Associates, a large single specialty group, since 1979
 - Clinical Professor in the Department of Internal Medicine at UT Southwestern Medical Center
 - Director of the Division of Rheumatology at Presbyterian Hospital, Dallas
 - Co-Medical Director of Metroplex Clinical Research Center
- Past president of the American College of Rheumatology and was honored in 2016 with the designation of Master by the American College of Rheumatology and in 2021 awarded the American College of Rheumatology Presidential Gold Medal for contributions to the field
- Completed a degree in biology from the University of Virginia and received his Doctor of Medicine with honors, from the University of Alabama School of Medicine in Birmingham. He completed an internship and residency in Internal Medicine at Parkland Memorial Hospital, Dallas, Texas, and a fellowship in Rheumatology at UT Southwestern/St. Paul University Hospital



There Is a High Need for Novel OAK Treatments Given the Lack of Durable Efficacy of Current Therapies and Frequent Progression to TKA

Unmet Need in OAK



Lack of effective treatment makes OAK a leading cause of chronic pain and disability, affecting >14 million patients in the United States¹⁻⁴



Oral NSAIDs have unfavorable safety profiles given long-term adverse effects (eg, GI ulcers, serious CV events)⁵



Current IA injections offer only short-term relief (eg, 3-6 months),⁶⁻⁹ and ≥ 12 months' durability is considered transformational



Lack of pharmacotherapy causes many patients to progress to TKA at an average cost of ~\$20,000 per procedure¹⁰

Opportunity for Novel Therapies



SoC largely consists of modalities that have existed for decades, and new MoAs are needed to advance patient care



Therapies providing durable pain relief could reduce disability (eg, patients with moderate-to-severe pain miss ~4 times more workdays than those with no or mild pain)¹¹⁻¹³



Novel treatments that reduce frequency of physician visits and surgery could lower the economic burden of OAK on the healthcare system

CV, cardiovascular; GI, gastrointestinal; IA, intraarticular; MoA, mechanism of action; NSAID, nonsteroidal anti-inflammatory drug; OAK, osteoarthritis of the knee; SoC, standard of care; TKA, total knee arthroplasty.

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PCRX-201, a Locally Administered Gene Therapy With an Inducible Promotor, Enables Production of IL-1Ra in the Target Joint Only When It Is Inflamed

PCRX-201 Construct



Adenovirus Vector

High-capacity, transduction efficient HCAAd with no viral coding sequences; carries the genetic code for IL-1Ra (ie, IL-1RA protein)



IL-1Ra

IL-1 is a known inflammatory cytokine with inhibition tied to the reduction of catabolic processes in the joint that contribute to OAK progression¹



Inducible Promoter

An NF-κB promotor turns on IL-1Ra production only in the presence of inflammation, mimicking the body's natural response to inflammation

Key PCRX-201 Strengths

Avoids Gene Therapy Pitfalls



PCRX-201 transduces at low doses and does not insert itself into the genome, mitigating safety concerns typically associated with gene therapies

Designed for Long-term Benefit



PCRX-201 enables joint cells to produce IL-1Ra, providing sustained levels of the protein to yield long-term therapeutic benefit

Protein Production Only As Needed



The inducible promotor allows for localized production of anti-inflammatory IL-1Ra where and when it is most needed, ensuring maintenance of joint homeostasis

Methods

This open-label phase 1 trial* (NCT04119687) enrolled 2 cohorts

Inclusion criteria

Adults aged 30-80 years with moderate-to-severe knee OA

- KL grade 2-4
- Prior treatment failure of ≥ 2 other therapies for OA
- Baseline WOMAC pain score ≥ 5.0 and ≤ 9.0 of 10.0

- Doses were assessed in cohort 1 first (part 1), followed by expansion with cohort 2 (part 2)
- Acetaminophen was the only permitted rescue analgesic through 52 weeks; oral NSAIDs, topical therapies, or topical cannabinoids were permitted only at investigator discretion after the first 60 days following treatment
- No other analgesics were permitted (other than stable doses of SSRIs, SNRIs, NSRIs, or tricyclics)

PCRX-201 dose:

Low: 1.4×10^{10} viral GC • Middle: 1.4×10^{11} viral GC • High: 1.4×10^{12} viral GC

Cohort 1: not pretreated (single ascending dose study)

PCRX-201 IA ultrasound-guided injection

Cohort 2: steroid pretreated (expansion)

IA methylprednisolone 40 mg immediately before PCRX-201 IA ultrasound-guided injection

Primary and secondary endpoints

- Safety assessments, repeated index knee assessments, laboratory evaluations, and biodistribution samples

Exploratory efficacy endpoints

- Patient-reported outcomes
 - WOMAC-A pain
 - WOMAC-B stiffness
 - KOOS subscale scores

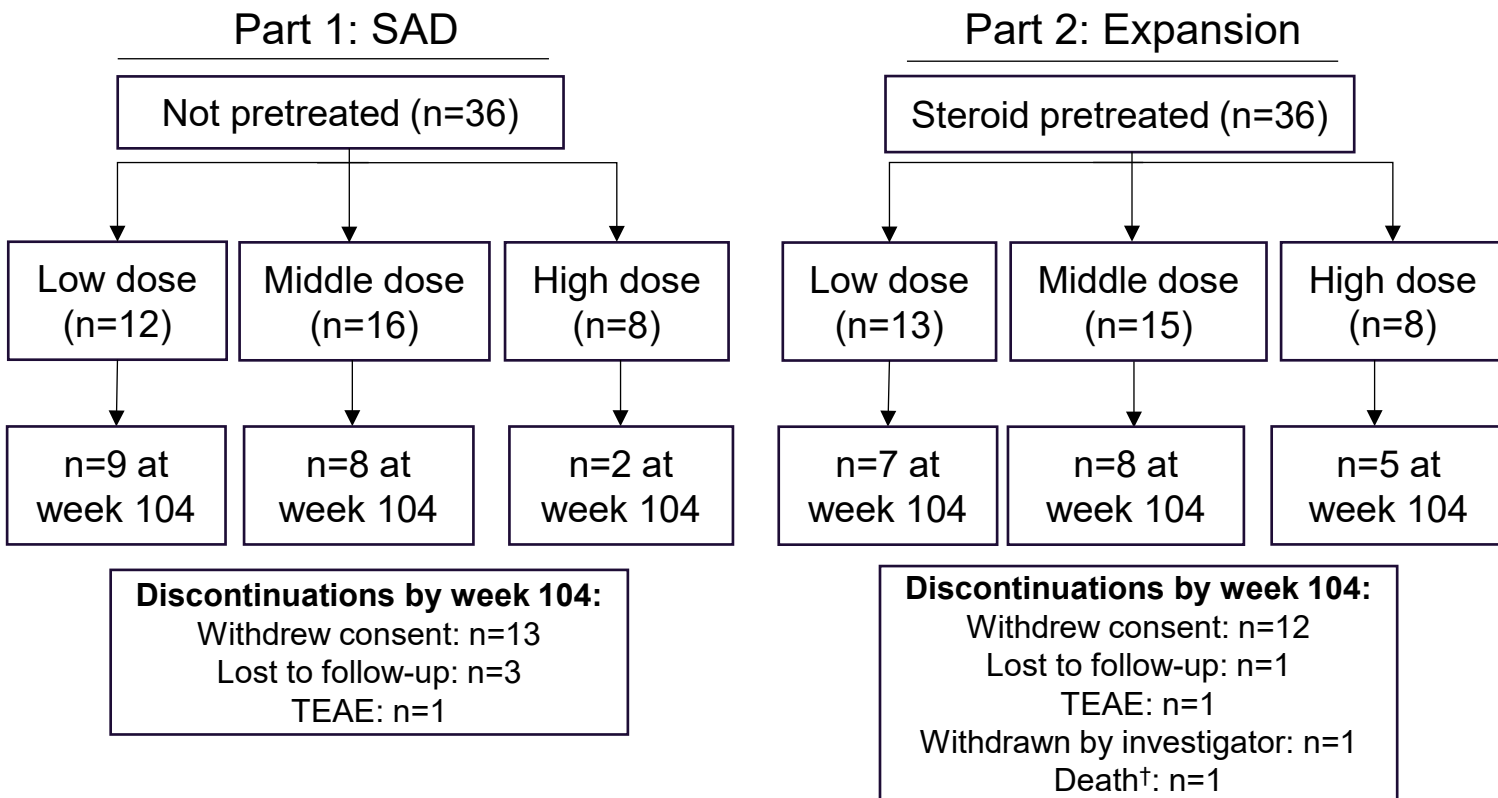
Structural assessments

- Joint space narrowing and width on fixed flexion radiograph
- MRI 3D femur bone shape (B-score)

Objective: to investigate the safety and efficacy up to 2 years of a single IA injection of PCRX-201 in participants with moderate-to-severe OAK in a phase 1 trial

The Median Follow-up of 72 Participants on Study Was 104 Weeks*

Participant flow diagram



- **72 individuals were treated**
 - 36 per cohort
- Median follow-up
 - **Not pretreated cohort:** 104 (range, 52-104) weeks
 - **Steroid pretreated cohort:** 104 (range, 65-104) weeks
- There were a similar number of discontinuations by week 104 in both groups
 - Dropout rates were consistent with rates observed in other osteoarthritis studies^{1,2}
- It is not likely that dropouts favorably biased the LSM results since LSM estimated the magnitude of a pain reduction to be smaller than the raw means (data not shown)

*Some participants discontinued at week 104 after providing data; in those cases, week-104 data are included in the analysis. Data were not imputed for missing values, and no data were carried forward. †Not considered related to the study treatment. LSM, least squares mean; SAD, single-ascending dose; TEAE, treatment-emergent adverse event; TKR, total knee replacement; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index. 1. Dougados et al. *Arthritis Rheum.* 2001;44(11):2539-2547; 2. Reginster et al. *Lancet.* 2001;357(9252):251-256.

Demographics and Baseline Characteristics Were Similar Across Cohorts

	Not pretreated cohort (n=36)	Steroid pretreated cohort (n=36)
Age, median (IQR), y	62.0 (58.5-67.0)	67.5 (58.5-71.5)
Women, n (%)	21 (58.3)	21 (58.3)
Race		
Asian	1 (2.8)	0
Black	4 (11.1)	4 (11.1)
White	31 (86.1)	32 (88.9)
KL grade, n (%)		
2	7 (19.4)	6 (16.7)
3	23 (63.9)	15 (41.7)
4	6 (16.7)	15 (41.7)
WOMAC pain score, mean (SD)	6.8 (1.3)	6.8 (1.1)
BMI, mean (SD), kg/m ²	32.1 (4.2)	31.2 (4.9)
Years since primary diagnosis, mean (SD)	8.6 (8.8)	14.6 (10.9)
Unilateral or bilateral OAK, n (%)		
Unilateral	8 (22.2)	10 (27.8)
Bilateral	28 (77.8)	26 (72.2)

- Baseline characteristics were similar across cohorts
 - Most participants were women with a KL grade of 3-4
 - Mean baseline WOMAC pain score was 6.8 in both cohorts
 - ~75% in both cohorts had bilateral OAK

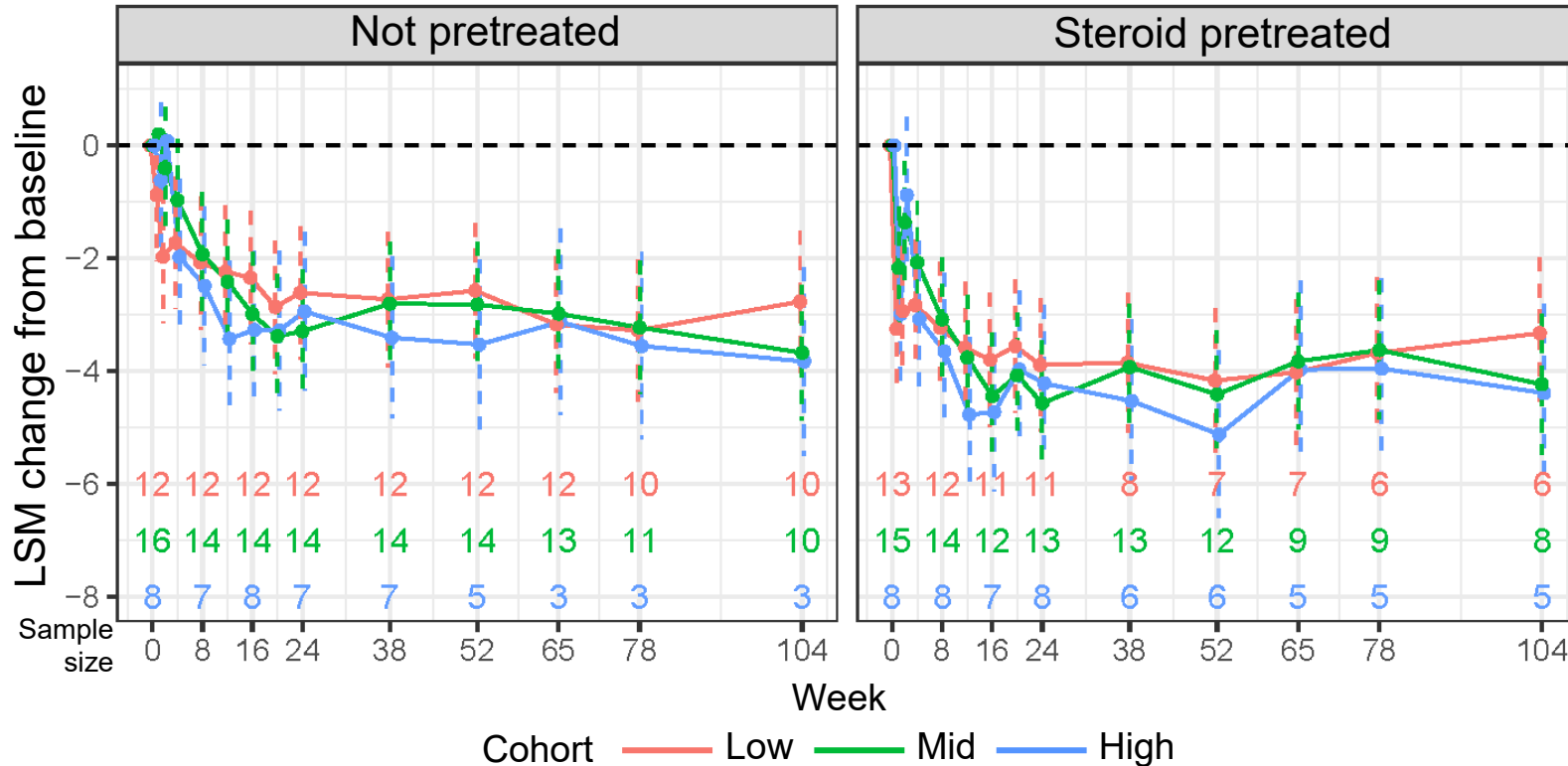
PCRX-201 Was Safe and Well-Tolerated Across a 100-Fold Range of Vector Doses

- No serious treatment-emergent AEs related to the treatment or procedure were reported regardless of steroid pretreatment or dose level
- Treatment-related joint effusion was the most common AE, with 61% (22/36) of participants in the not pretreated cohort and 36% (13/36) of participants in the steroid pretreated cohort having a treatment-related joint effusion
 - Treatment-related joint effusions were more frequent and severe in the not pretreated cohort
 - Treatment-related joint effusions had similar durations in both cohorts* (median 18 days [range, 2-165 days] in the not pretreated cohort and median 33 days [range, 3-111 days] in the steroid pretreated cohort)

Summary of Participants With TEAEs [†]								
	Not pretreated cohort (n=36)				Steroid pretreated cohort (n=36)			
	Low dose (n=12)	Middle dose (n=16)	High dose (n=8)	Total	Low dose (n=13)	Middle dose (n=15)	High dose (n=8)	Total
Any TEAE	11 (91.7)	16 (100)	8 (100)	35 (97.2)	12 (92.3)	14 (93.3)	8 (100)	34 (94.4)
SAE	2 (16.7)	1 (6.3)	1 (12.5)	4 (11.1)	1 (7.7)	2 (13.3)	2 (25.0)	5 (13.9)
TEAE grade ≥3	3 (25.0)	3 (18.8)	3 (37.5)	9 (25.0)	2 (15.4)	4 (26.7)	2 (25.0)	8 (22.2)
Participants with TEAEs occurring in ≥10% of participants in either cohort								
Arthralgia	5 (41.7)	4 (25.0)	1 (12.5)	10 (27.8)	5 (38.5)	5 (33.3)	6 (75.0)	16 (44.0)
Headache	2 (16.7)	1 (6.3)	2 (25.0)	5 (13.9)	1 (7.7)	2 (13.3)	1 (12.5)	4 (11.1)
Hypertension	2 (16.7)	2 (12.5)	0 (0)	4 (11.1)	0 (0)	0 (0)	0 (0)	0 (0)
Joint effusion	6 (50.0)	10 (62.5)	8 (100)	24 (66.7)	5 (38.5)	5 (33.3)	5 (62.5)	15 (41.7)
Joint swelling	7 (58.3)	1 (6.3)	1 (12.5)	9 (25.0)	0 (0)	0 (0)	0 (0)	0 (0)
Synovial cyst	3 (25.0)	1 (6.3)	1 (12.5)	5 (13.9)	0 (0)	0 (0)	0 (0)	0 (0)
Back pain	0 (0)	0 (0)	0 (0)	0 (0)	2 (15.4)	1 (6.7)	1 (12.5)	4 (11.1)
Fall	0 (0)	0 (0)	0 (0)	0 (0)	2 (15.4)	3 (20.0)	0 (0)	5 (13.9)
Musculoskeletal pain	0 (0)	0 (0)	0 (0)	0 (0)	2 (15.4)	0 (0)	2 (25.0)	4 (11.1)
Osteoarthritis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (13.3)	2 (25.0)	4 (11.1)

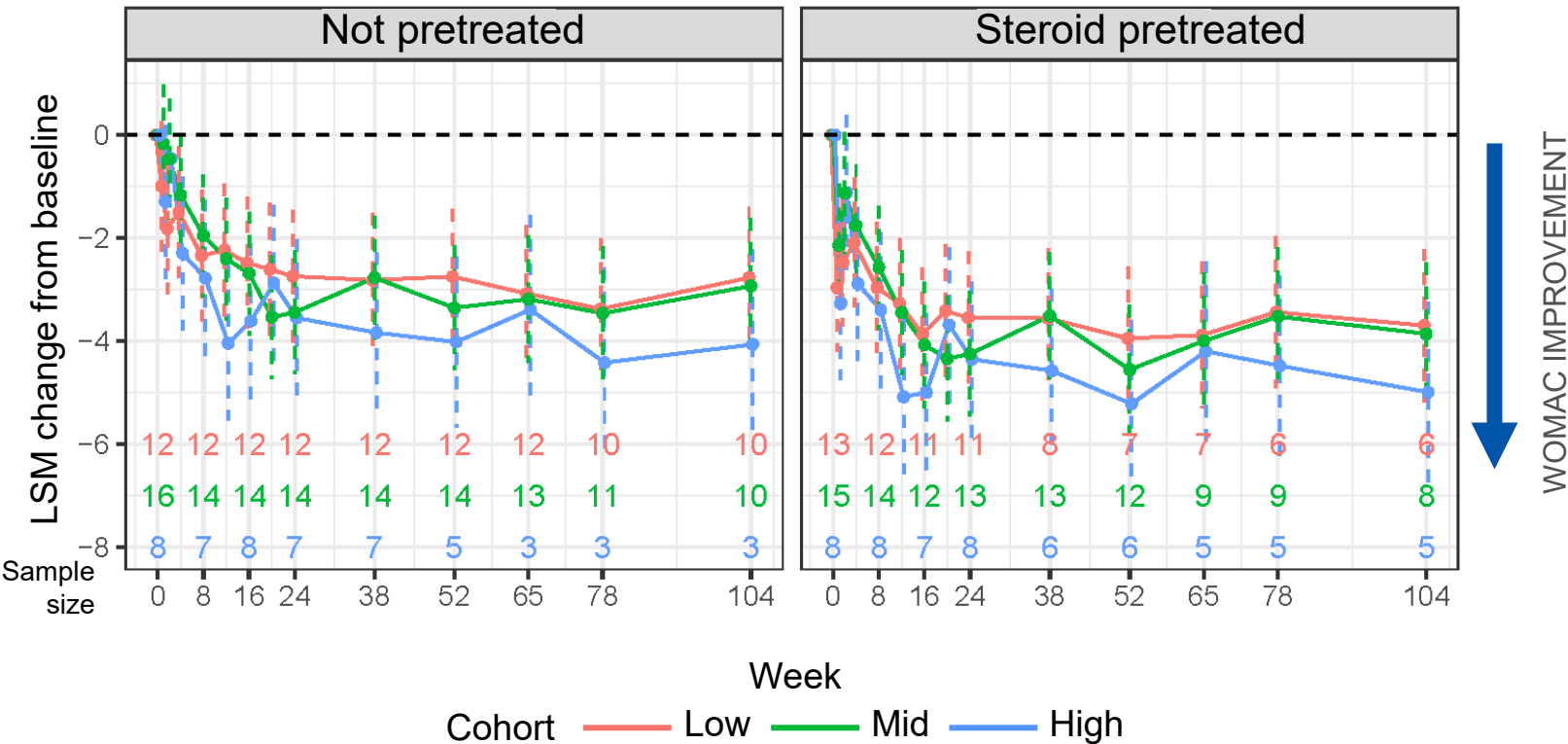
AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event. *Effusion end was only adjudicated during scheduled visits, rather than self-reported, which may have increased the estimated duration for participants depending on visit schedule. [†]Including all TEAEs related and unrelated to treatment. AE grading was performed according to CTCAE v5.0.

Efficacy–WOMAC-A Pain: Sustained Improvement at 104 Weeks



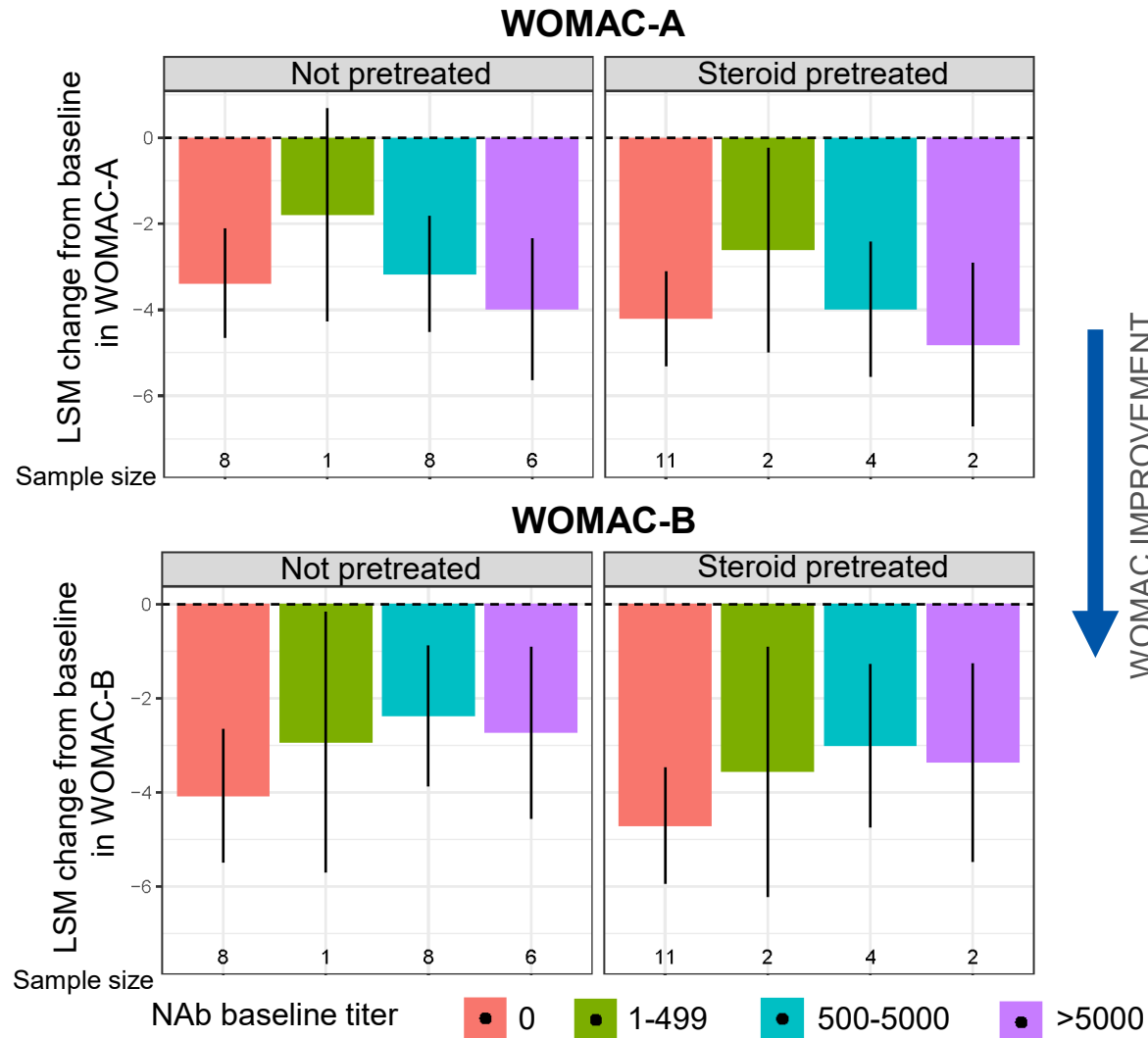
- There was considerable improvement compared with baseline in WOMAC-A pain at all dose levels
 - Improvement in pain was greatest with steroid pretreatment
 - Similar results were seen with percent reduction from baseline
 - A 48%-65% reduction from baseline pain was observed in the steroid pretreated cohort across all dose levels, and a 41%-58% reduction from baseline pain was observed in the not pretreated cohort across all dose levels

Efficacy–WOMAC-B Stiffness: Sustained Improvement at 104 Weeks



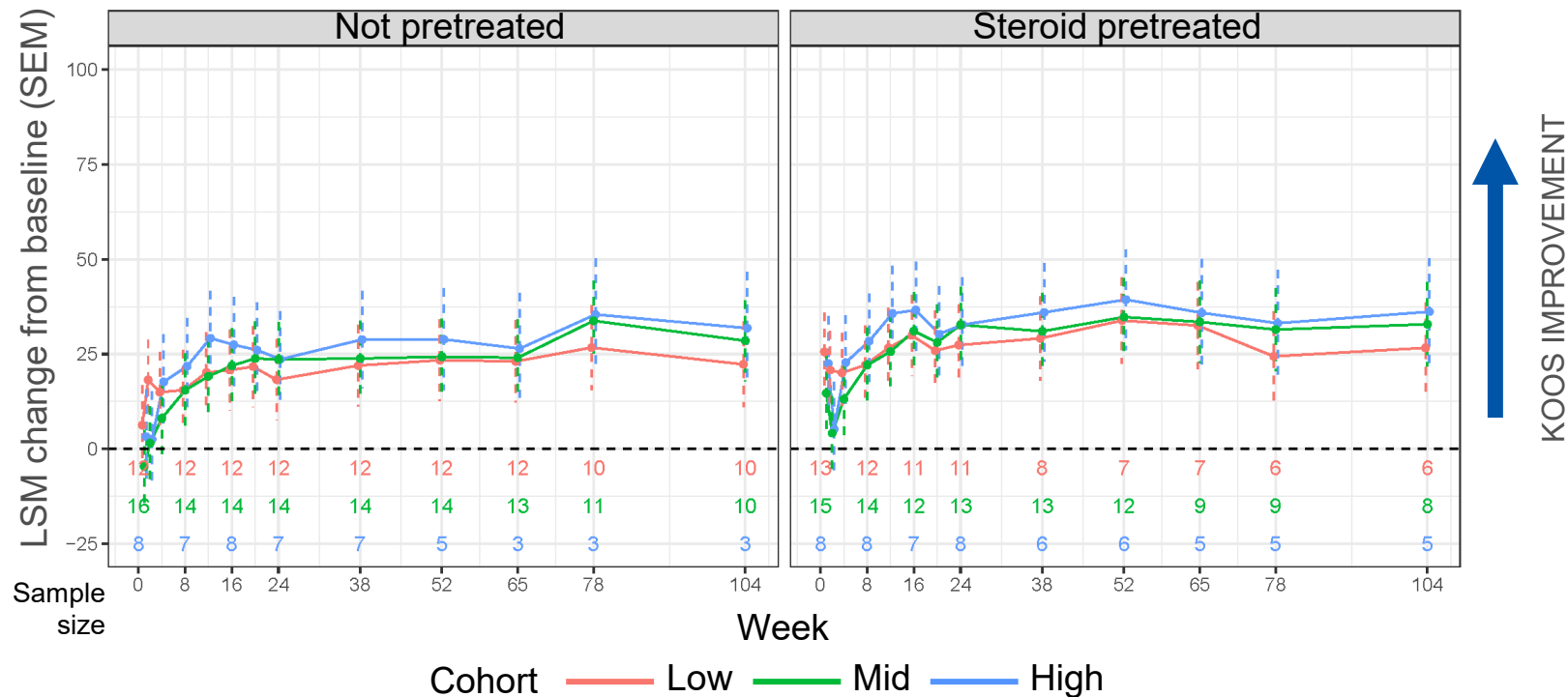
- Similar improvement compared with baseline was observed in WOMAC-B stiffness at all dose levels
 - Improvement in stiffness was greatest with steroid pretreatment
 - Similar results were seen with percent reduction from baseline
 - A 53%-72% reduction from baseline stiffness was observed in the steroid pretreated cohort across all dose levels, and a 33%-53% reduction from baseline stiffness was observed in the not pretreated cohort across all dose levels

Neutralizing Antibodies: No Impact of Baseline NABs on Safety or Efficacy Regardless of Baseline NAb titer*



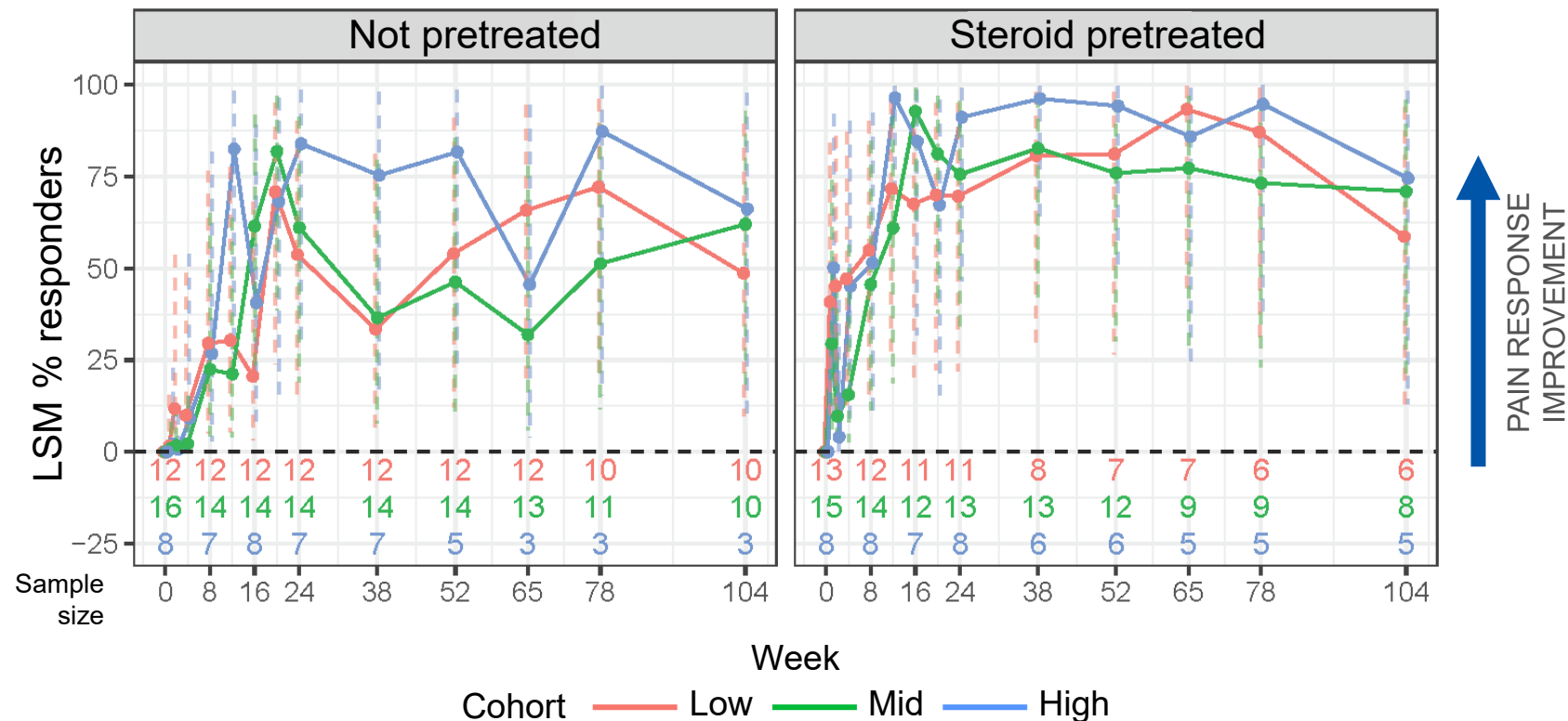
- For participants with valid NAb samples, baseline NAb positivity was 67% (8/12), 62% (10/16), and 62% (5/8) for the low, medium, and high doses, respectively, in the not pretreated cohort and 62% (8/13), 27% (4/15), and 12% (1/8) for the low, medium, and high doses, respectively, in the steroid pretreated cohort
- The presence of baseline NABs did not impact WOMAC-A pain scores or WOMAC-B stiffness scores at 104 weeks

Efficacy– KOOS Activities of Daily Living Function Scores: Sustained Improvement at 104 Weeks



- There were favorable improvements in KOOS activities of daily living scores at all dose levels
 - There was a greater improvement in the steroid pretreated cohort (26.6 to 36.2 of 100 points across doses) compared with the not pretreated cohort (22.3 to 31.8 of 100 points across doses)
- Other KOOS subscales showed similar improvement, with the pretreated cohort having slightly higher KOOS scores than the not pretreated cohort

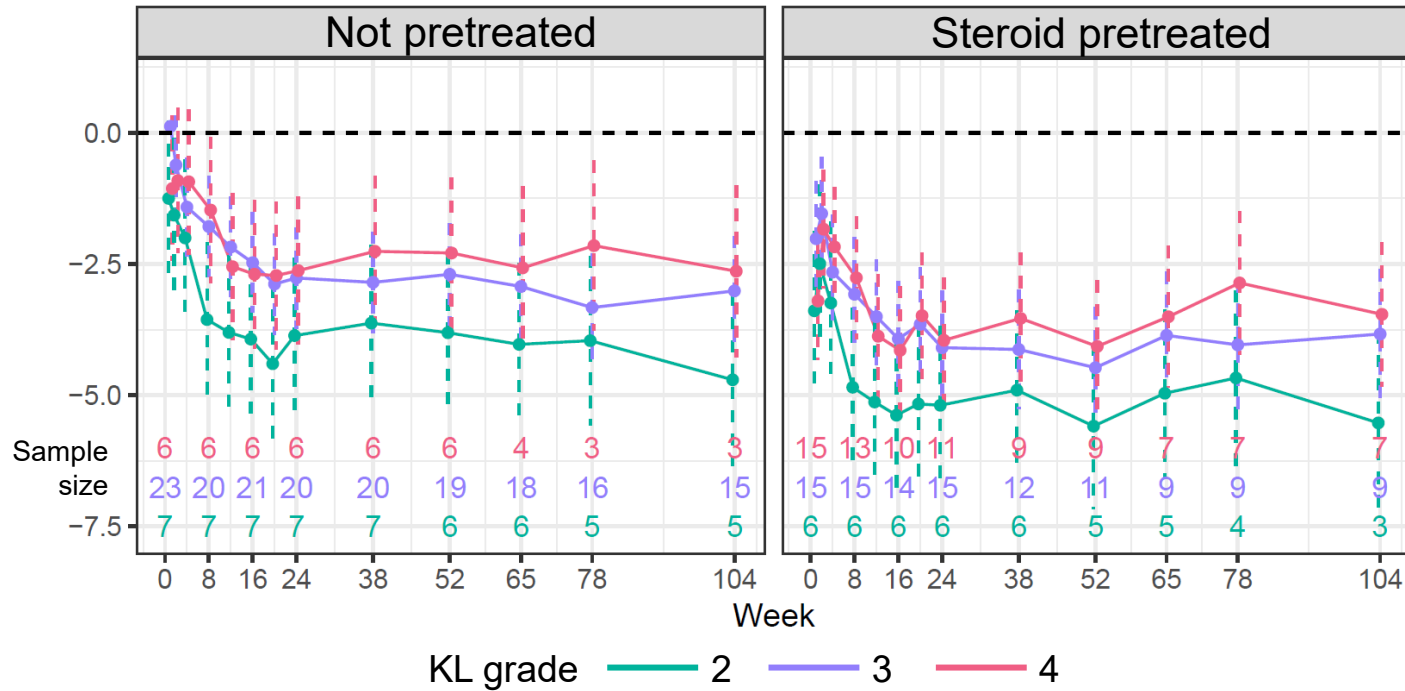
Efficacy—WOMAC-A Pain: More Percent Responders at 104 Weeks in the Steroid Pretreated Group



- >50% of participants in the not pretreated cohort had a pain response (defined as $\geq 50\%$ reduction in WOMAC-A from baseline) by 24 weeks
- >40% of participants in the steroid pretreated cohort had a pain response as early as 2 to 8 weeks, and >70% of participants had a pain response by 16 weeks

Efficacy–WOMAC-A Pain by Baseline KL Grade

LSM change from baseline



WOMAC IMPROVEMENT

- Participants in the not pretreated cohort with KL grade 2 had the largest LSM reduction from baseline in WOMAC-A pain (4.7 points), but participants with KL grade 3 or 4 also had reductions from baseline (3.0 and 2.6, respectively)
- Participants in the steroid pretreated cohort with KL grade 2 had the largest LSM reduction from baseline in WOMAC-A pain (5.5 points), but participants with KL grade 3 or 4 also had reductions (3.8 and 3.5, respectively)

Disease Progression With PCRX-201 Did Not Differ From Natural Progression at 104 Weeks

- MRI B-score change from baseline ranged from 2.3 to 5.4 in the not pretreated cohort and from 2.6 to 5.9 in the steroid pretreated cohort
- Joint space narrowing and width had a wider range for the not pretreated cohort

	Joint space narrowing	Joint space width
Not pretreated cohort	-0.08 to 0.03 mm	-0.27 to -0.03 mm
Steroid pretreated cohort	-0.14 to 0 mm	-0.05 to 0.13 mm

Conclusions

- 1 A single intraarticular injection of PCRX-201 had acceptable safety with improvements in pain, stiffness, and function across KL grades to 104 weeks, indicating a potential for sustained clinical efficacy in patients with moderate-to-severe OAK
- 2 The steroid pretreated cohort had fewer joint effusions and more pain reduction than the not pretreated cohort, suggesting that steroid pretreatment may favorably affect efficacy and safety/tolerability
 - Steroid pretreatment may have a favorable impact on PCRX-201 performance with respect to safety and efficacy through 104 weeks
- 3 Structural assessment in these small cohorts at week 104 demonstrated that disease progression with PCRX-201 did not differ significantly from expected natural progression; however, longer follow-up is needed
- 4 These promising results support further investigation of PCRX-201 with steroid pretreatment in OAK in randomized, double-blind, active-controlled studies planned for 2025

Thank you!

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