Dose Response, Immunogenicity, and Clinical Outcomes Following Intraarticular IL-1RA Gene Therapy (PCRX-201) in Knee Osteoarthritis: a Phase 1 Study With 104-Week Follow-up

Stanley Cohen, MD[1]; Philip G. Conaghan, MBBS, PhD[2]; Warren Rizzo, MD[3]; MiJeong Kim, PhD[3]; Nino Joy, MD[3]; Lucia Sanchez-Gonzalez, MPH[3*]; Mary DiGiorgi, PhD, MPH[3]; Jonathan Slonin, MD, MBA[3]; Derek Jackson, MA[3]

[1]Metroplex Clinical Research Center, Dallas, TX; [2]University of Leeds, West Yorkshire, United Kingdom; [3]Pacira BioSciences, Inc., Brisbane, CA

*Affiliation at the time of study.

PURPOSE

To evaluate the immunogenicity of PCRX-201 and its impact on dose-related immune responses and clinical outcomes through 104 weeks after intra-articular (IA) administration, and to examine the PCRX-201 dose response

CONCLUSIONS

1. PCRX-201 demonstrated improvements in clinical outcomes and a tolerable safety profile with no evidence of immunogenicity-related serious adverse events (SAEs)
2. Although PCRX-201 injection resulted in the induction of anti–adenovirus serotype 5 (Ad5) neutralizing antibodies (NAbs), clinical outcomes were durable and unaffected
3. The inflammation-inducible promoter of PCRX-201 is hypothesized to limit uncontrolled immune activation, preventing off-target effects
4. The highest dose of PCRX-201 did not result in better clinical outcomes than lower doses, with an increase in AEs; thus, ongoing investigations including a phase 2 trial focus on low- to middle-dose levels to optimize the benefit-risk ratio and minimize the potential for AEs

PRESENTER: Stanley Cohen; stanley.cohen@dfwra.com.

ROLE OF THE STUDY SPONSOR: This study was funded by Pacira Biosciences, Inc. Pacira BioSciences, Inc designed the study and was involved in data collection, analysis, and interpretation. Medical writing support was provided by Fingerpaint Medical at the direction of the authors and was funded by Pacira BioSciences, Inc. All authors had full access to data, participated in manuscript development, approved final content, and had final responsibility for the decision to publish.

DISCLOSURES: SC is a consultant and investigator for Pacira BioSciences, Inc. PGC has received consulting fees from AbbVie, AstraZeneca, Biosplice, Eli Lilly, Formation Bio, Genascence, Grunenthal, Kolon TissueGene, Levicept, Moebius, Novartis, Orion, Pacira BioSciences, Stryker, and Takeda. **WR, MJK, NJ, LS-G, MDG, JS,** and **DJ** are employees of Pacira BioSciences, Inc, and may hold stock or stock options in the company.

Presented at the American College of Rheumatology Convergence; November 6-11, 2026; Orlando, FL.

BACKGROUND

- Knee OA is a common and severe disease that affects 365 million people worldwide and 14%-37% of adults in the United States since 1980, with prevalence increasing substantially with age[1,2]
- The inflammatory cytokine IL-1 is overexpressed in knee OA and is one of the key drivers of disease progression[3-7]
  - Although reduced rates of joint replacement have been suggested in some studies of prolonged anti–IL-1 therapy, knee OA trials targeting IL-1 have exhibited limited efficacy, partly attributable to the short half-lives of the treatments studied[8,9]
- Gene therapy is under investigation as a potential treatment for knee OA that potentially could offer longer pain relief than the pain benefits lasting ≤3 months with standard IA glucocorticoid injections[10-13]
- A common issue associated with gene therapies is the development of immunogenicity such as neutralization and clearance, which, as a result, can compromise the safety, efficacy, and long-term durability of gene therapies[14]
- PCRX-201 is an IA gene therapy designed to enable inflammation-inducible expression of IL-1 receptor antagonist (IL-1Ra) in knee OA[15]
- We evaluated the immunogenicity of PCRX-201 and its impact on dose response and clinical outcomes through 104 weeks after injection
  - IL-1Ra expression is likely to change depending on the local inflammation status
  - The PCRX-201 promoter is inflammation responsive and so is driven by inflammatory activity rather than vector dose.[16,17] Transgene expression levels dynamically rise during flares and subside as joint inflammation abates, closely mirroring the natural physiologic response of the body[17]
  - Therefore, a traditional linear dose response is not expected with PCRX-201
- Pretreatment with glucocorticoids may enhance gene transfer[18,19]

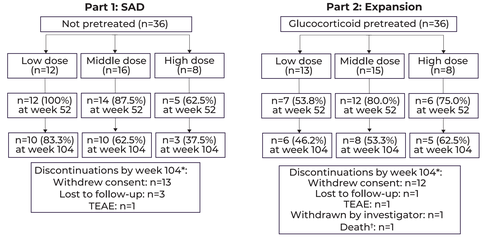
METHODS

- This phase 1 open-label study (NCT04119687) enrolled adults aged 30-80 years with symptomatic knee OA into 2 cohorts
  - Symptomatic knee OA was defined as WOMAC pain ≥5 to ≤9 and Kellgren-Lawrence grade 2 to 4 or who met the 1986 ACR Classification Criteria of the Knee
  - The first cohort (single ascending dose) received ultrasound-guided IA injection of PCRX-201 in the index knee at 1 of 3 doses (1.4×10^{10}, 1.4×10^{11}, or 1.4×10^{12} genome copies)
  - The second cohort received pretreatment with glucocorticoids (IA methylprednisolone acetate 40 mg) immediately before PCRX-201 injection at the same 3 doses
- Immunogenicity endpoints included serum and synovial fluid anti-Ad5 NAb titers and serum anti–IL-1Ra antibody titers
- Clinical outcomes including WOMAC pain, WOMAC stiffness, Knee Injury and Osteoarthritis Outcome Score (KOOS) activities of daily living, safety, and biodistribution were assessed through 104 weeks

RESULTS

- A total of 72 patients were enrolled in this study, 36 each in the not pretreated and glucocorticoid pretreated groups (Figure 1)

Figure 1. Patient flow diagram.



*Some patients discontinued at week 104 after providing data; in those cases, data from week 104 are included in the analysis. †Death was from natural causes, not considered related to study treatment.
SAD, single ascending dose; TEAE, treatment-emergent adverse event. Adapted from Cohen et al. Safety, biodistribution, and exploratory clinical outcomes of a novel intra-articular IL-1Ra gene therapy (PCRX-201) in moderate-to-severe knee osteoarthritis: 2-year results of a phase 1 study. *Ann Rheum Dis*, 2026. doi: 10.1016/j.ard.2026.06.034, under Creative Commons Attribution NonCommercial – NoDerivs (CC BY-NC-ND 4.0).[17]

- Patients were a mean age of 63.6 years, 58.3% women, and 87.5% white (Table 1)

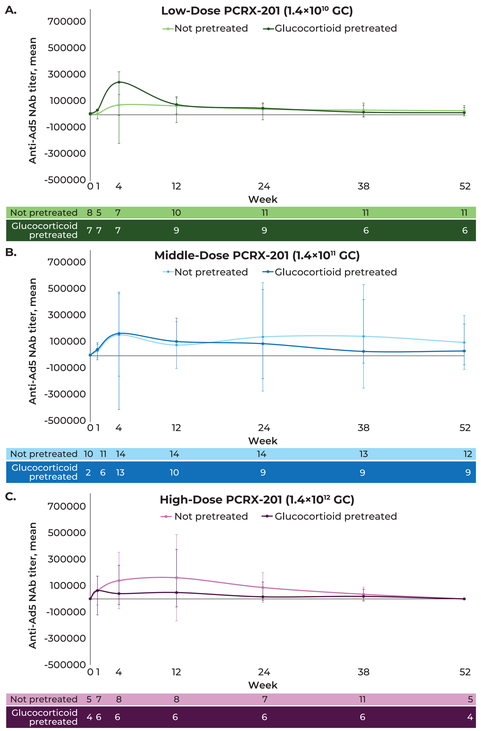
Table 1. Patient Demographics and Baseline Characteristics

	Not pretreated group (n=36)			Glucocorticoid pretreated group (n=36)			All (N=72)
	Low dose (n=12)	Middle dose (n=16)	High dose (n=8)	Low dose (n=13)	Middle dose (n=15)	High dose (n=8)	Total
Age, mean (SD), y	62.6 (7.3)	62.3 (8.0)	62.4 (10.5)	64.5 (11.7)	64.7 (10.7)	65.3 (7.2)	63.6 (9.2)
Women, n (%)	7 (58.3)	8 (50.0)	6 (75.0)	9 (69.2)	8 (53.3)	4 (50.0)	42 (58.3)
Race							
Asian	0	1 (6.3)	0	0	0	0	1 (1.4)
Black	1 (8.3)	2 (12.5)	1 (12.5)	2 (15.4)	1 (6.7)	1 (12.5)	8 (11.1)
White	11 (91.7)	13 (81.3)	7 (87.5)	11 (84.6)	14 (93.3)	7 (87.5)	63 (87.5)
K-L grade, n (%)							
2	3 (25.0)	2 (12.5)	2 (25.0)	2 (15.4)	2 (13.3)	2 (25.0)	13 (18.1)
3	7 (58.3)	11 (68.8)	5 (62.5)	5 (38.5)	8 (53.3)	2 (25.0)	38 (52.8)
4	2 (16.7)	3 (18.8)	1 (12.5)	6 (46.2)	5 (33.3)	4 (50.0)	21 (29.2)
BMI, mean (SD), kg/m^2	31.4 (4.2)	32.2 (4.7)	32.9 (2.6)	30.1 (5.6)	32.9 (4.5)	29.6 (3.8)	31.6 (4.5)
Years since primary diagnosis, mean (SD)	7.1 (5.2)	9.9 (12.0)	8.5 (4.8)	17.3 (13.4)	14.1 (10.0)	10.9 (7.4)	11.6 (10.2)
Unilateral or bilateral knee OA, n (%)							
Unilateral	1 (8.3)	3 (18.8)	4 (50.0)	4 (30.8)	4 (26.7)	2 (25.0)	18 (25.0)
Bilateral	11 (91.7)	13 (81.3)	4 (50.0)	9 (69.2)	11 (73.3)	6 (75.0)	54 (75.0)
WOMAC pain scores,[a] mean (SD)	6.3 (1.2)	6.6 (1.1)	6.4 (0.5)	6.7 (1.1)	6.8 (1.0)	7.0 (0.9)	6.6 (1.0)

[a]WOMAC total score range, 0-10; lower scores indicate less pain. BMI, body mass index; K-L, Kellgren-Lawrence; SD, standard deviation. Adapted from Cohen et al. Safety, biodistribution, and exploratory clinical outcomes of a novel intra-articular IL-1Ra gene therapy (PCRX-201) in moderate-to-severe knee osteoarthritis: 2-year results of a phase 1 study. *Ann Rheum Dis*, 2026. doi: 10.1016/j.ard.2026.06.034, under Creative Commons Attribution NonCommercial – NoDerivs (CC BY-NC-ND 4.0).[17]

- Patients across all 3 dose levels of PCRX-201 had anti-Ad5 NAb titers that peaked at 4-12 weeks and resolved thereafter (Figure 2)
- Glucocorticoid pretreatment lowered anti-Ad5 NAb titer at later time points, particularly for patients who received high-dose PCRX-201 (Figure 2)

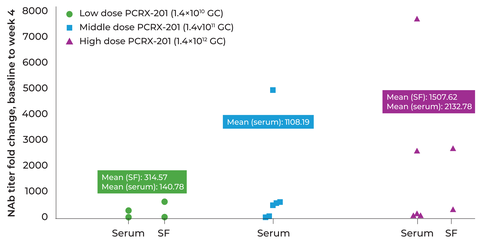
Figure 2. Mean (SD) serum anti-Ad5 NAb titer by (A) low, (B) middle, and (C) high dose in the not pretreated and glucocorticoid pretreated groups.



Error bars are the standard deviation. Ad5, adenovirus serotype 5; GC, genome copies; NAb, neutralizing antibody.

- At week 4, similar increases in anti-Ad5 NAb titers were observed in 15 patients who had both baseline and Week 4 serum or synovial fluid assessments following PCRX-201 injection (Figure 3)

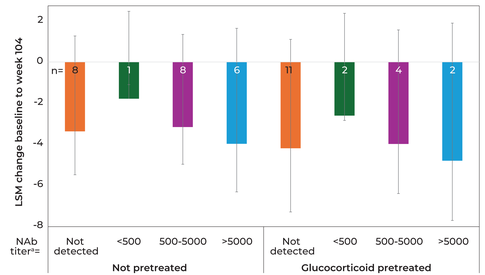
Figure 3. Increase in anti-Ad5 NAb titers from baseline to week 4 in serum and synovial fluid following a single intraarticular injection of PCRX-201 at low, middle, and high doses.



[a]Patients with serum NAbs were distinct from those with SF NAbs in the low-dose PCRX-201 group. [b]These 2 patients also had serum NAbs in the high-dose PCRX-201 group. The fold change calculation was performed only using data with matching serum and/or synovial fluid values (ie, both baseline and week-4 values). Note that only the not pretreated cohort had synovial fluid data available.Ad5, adenovirus serotype 5; GC, genome copies; NAb, neutralizing antibody; SF, synovial fluid.

- Despite the presence of baseline anti-Ad5 NAb titers (which can affect transduction and subsequent gene expression), clinical outcomes were unaffected (Figure 4)
- No strong dose response was observed in either treatment group

Figure 4. LSM change from baseline to week 104 in WOMAC pain score by baseline anti-Ad5 NAb titer.



[a]At baseline. Error bars are the 95% CI. CI, confidence interval; LSM, least squares mean; NAb, neutralizing antibody; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

- Of the 72 patients in the study, 1 treated with high-dose PCRX-201 had detectable baseline serum levels of anti–IL-1Ra antibodies, which were no longer detectable between weeks 12 and 24. By week 12, a patient treated with middle-dose PCRX-201 had detectable levels of anti–IL-1Ra antibodies at week 4, which were no longer detectable between weeks 38 and 52; both of these patients were from the not pretreated group
  - The presence of these antibodies did not seem to affect pain scores
- PCRX-201 remained localized, with minimal systemic exposure outside the index knee joint. Structural outcomes determined by radiographic changes showed no progression beyond that expected over 104 weeks in knee OA
- The most common AE was transient knee effusion in the index knee reported by 24 patients (66.7%) in the not pretreated group and 15 patients (41.7%) in the glucocorticoid pretreated group. No immune-mediated SAEs were reported (Table 2)

Table 2. Summary of TEAES

	Not pretreated group (n=36)			Glucocorticoid pretreated group (n=36)			All (N=72)
	Low dose (n=12)	Middle dose (n=16)	High dose (n=8)	Low dose (n=13)	Middle dose (n=15)	High dose (n=8)	Total
Any TEAE	11 (91.7)	16 (100.0)	8 (100.0)	12 (92.3)	14 (93.3)	8 (100)	69 (95.8)
SAE	2 (16.7)	1 (6.3)	1 (12.5)	1 (7.7)	2 (13.3)	2 (25.0)	9 (12.5)
TEAE grade ≥3	3 (25.0)	3 (18.8)	3 (37.5)	2 (15.4)	4 (26.7)	2 (25.0)	17 (23.6)
TEAE occurring in ≥10% of patients							
Joint effusion	6 (50.0)	10 (62.5)	8 (100)	5 (38.5)	5 (33.3)	5 (62.5)	39 (54.2)
Arthralgia	6 (50.0)	4 (25.0)	1 (12.5)	5 (38.5)	5 (33.3)	6 (75.0)	27 (37.5)
Joint swelling	7 (58.3)	1 (6.3)	1 (12.5)	0	2 (13.3)	0	11 (15.3)
Headache	2 (16.7)	0	2 (25.0)	1 (7.7)	2 (13.3)	1 (12.5)	8 (11.1)

Values are the number (percentage) of patients experiencing events (patients may experience >1 event). SAE, serious adverse event; TEAE, treatment-emergent adverse event. Reproduced from Cohen et al. Safety, biodistribution, and exploratory clinical outcomes of a novel intra-articular IL-1Ra gene therapy (PCRX-201) in moderate-to-severe knee osteoarthritis: 2-year results of a phase 1 study. *Ann Rheum Dis*, 2026. doi: 10.1016/j.ard.2026.06.034, under Creative Commons Attribution NonCommercial – NoDerivs (CC BY-NC-ND 4.0).[17]

REFERENCES: 1. Lawrence et al. *Arthritis Rheum*. 2008;58(1):26-35. **2.** Long et al. *Arthritis Rheumatol*. 2022;74(7):1172-1183. **3.** Evans et al. *Gene Ther*. 2004;11(4):379-389. **4.** Mehta et al. *Curr Opin Rheumatol*. 2021;33(1):94-109. **5.** Kapoor et al. *Nat Rev Rheumatol*. 2011;7(1):33-42. **6.** Saha et al. *Arthritis Rheum*. 1999;42(8):1577-1587. **7.** Smith et al. *J Rheumatol*. 1997;24(2):365-371. **8.** Daheshia H, Yao JQ. *J Rheumatol*. 2008;35(12):2306-2312. **9.** Chevalier et al. *Arthritis Rheum*. 2009;61(3):344-352. **10.** American Academy of Orthopaedic Surgeons. American Academy of Orthopaedic Surgeons Management of Osteoarthritis of the Knee (Non-Arthroplasty) Evidence-Based Clinical Practice Guideline. https://www.aaos.org/oak3cpg. Published 2021. Updated August 31, 2021. Accessed March 20, 2025. **11.** Li et al. *Precis Clin Med*. 2023;6(2):pbad014. **12.** Nixon et al. *Arthritis Rheumatol*. 2018;70(11):1757-1768. **13.** Schieker et al. *Ann Intern Med*. 2020;173(7):509-515. **14.** US Food and Drug Administration. Immunogenicity of gene therapy products. Silver Spring, MD: FDA; June 29, 2026. Accessed September 10, 2026. https://www.fda.gov/vaccines-blood-biologics/science-research-biologics/immunogenicity-gene-therapy-products. **15.** Senter et al. *Hum Gene Ther*. 2022;33(9-10):541-549. **16.** Uebelhoer et al. *Front Med (Lausanne)*. 2026;10:1148623. **17.** Cohen et al. *Ann Rheum Dis*. 2026. doi: 10.1016/j.ard.2026.06.034. **18.** Seregin et al. *Mol Ther*. 2009;17(4):685-696. **19.** Price et al. *Gene Ther*. 2007;14(22):1594-1604.