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Intraarticular Injection of PCRX-201 Gene Therapy Was Safe and Had Clinical Benefits Through 3 Years in Patients With Knee Osteoarthritis

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OBJECTIVES

To assess the impact of PCRX-201 gene therapy on pain, stiffness, and function in patients with knee osteoarthritis (OA) stratified by structural severity (assessed by Kellgren-Lawrence [K-L] grade) after 156 weeks

CONCLUSIONS

1. A single intraarticular (IA) injection of PCRX-201 was safe and led to improvements in pain, stiffness, and function for up to 156 weeks in most structural severity subgroups
2. The greatest improvements were observed in individuals with K-L grade 2; however, improvements were also observed for those with K-L grade 3 or 4, suggesting PCRX-201 may be useful across the spectrum of knee OA severity
3. These data warrant further investigation in an ongoing randomized, double-blind, active-controlled phase 2 study (NCT06884865)

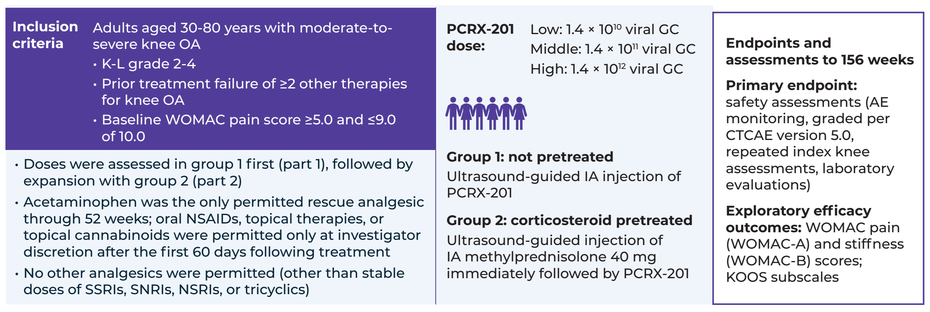
INTRODUCTION

- Safe and effective treatments for knee OA that provide long-term improvements in pain and function are needed because current treatments provide only short-term relief [1]
  - Specifically, there is an unmet need for treatment options for patients with moderate-to-severe knee OA (ie, K-L grade 3 or 4) who have higher pain and worse function than those with less severe structural disease[2,3]
- PCRX-201 is a high-capacity (HCAd), nonintegrating, nonreplicating adenovirus serotype 5 vector for IA injection. Following PCRX-201 injection, cells transduced with PCRX-201 express human interleukin-1 receptor antagonist, an interleukin-1 signaling inhibitor[4]
  - PCRX-201 is under the control of an inducible promoter that is active only when local inflammation is present in the target knee, thereby mimicking the body's natural response to inflammation[4]
  - Interim data from an ongoing phase 1b study suggested that PCRX-201 exhibited an acceptable safety profile and improvements in pain, stiffness, and function to 156 weeks after injection

METHODS

- This open-label phase 1 trial (NCT04119687) enrolled 2 groups (Figure 1)
  - The first group received ultrasound-guided IA injection of PCRX-201 in the target knee at 1 of 3 doses (low, middle, or high)
  - The second group received ultrasound-guided IA injection consisting of pretreatment with methylprednisolone 40 mg immediately before PCRX-201 at the same low, middle, or high doses to explore the benefit of immune modulation to maximize vector tolerability and transduction
- The current post hoc analysis has a median follow-up of 156 weeks and examines results by K-L grade up to 156 weeks after injection

Figure 1. Study design.



AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; GC, genome copies; IA, intraarticular; K-L, Kellgren-Lawrence; KOOS, Knee Injury and Osteoarthritis Outcome Score; NSAID, nonsteroidal anti-inflammatory drug; NSRI, nonselective serotonin reuptake inhibitor; OA, osteoarthritis; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

RESULTS

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

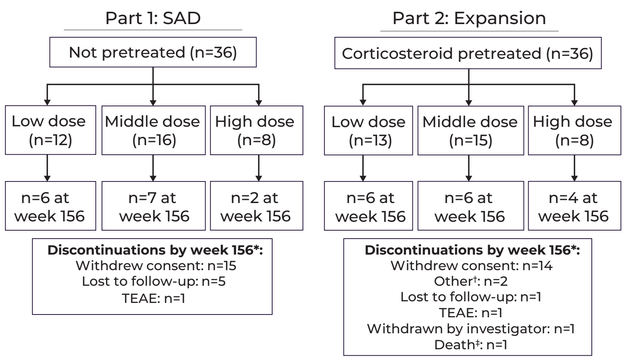
- Overall, 36 participants were enrolled and treated in each group (Figure 2)
- Participant demographics and baseline characteristics were similar across groups (Table)
- There was a similar number of discontinuations by week 156 in both groups (Figure 2)

Table. Participant Demographics and Baseline Characteristics

	Not pretreated group (n=36)	Corticosteroid pretreated group (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)
K-L grade, n (%)		
2	7 (19.4)	6 (16.7)
3	23 (63.9)	15 (41.7)
4	6 (16.7)	15 (41.7)
WOMAC-A pain score, mean (SD)	6.4 (1.0)	6.8 (1.0)
Follow-up, median (range) wk	142.5 (15-156)	127 (8.156)

IQR, interquartile range; K-L, Kellgren-Lawrence; SD, standard deviation.

Figure 2. Participant flow diagram.

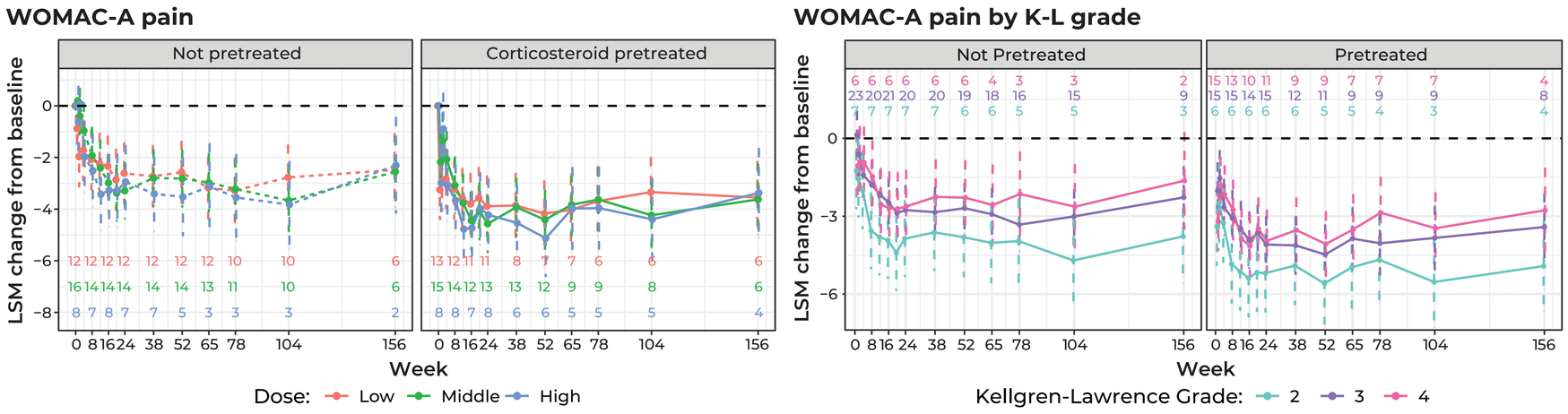


SAD, single ascending dose; TEAE, treatment-emergent adverse event. *Some participants discontinued at week 156 after providing data; in those cases, week-156 data are included in the analysis. †One participant discontinued because of progression to total knee arthroplasty, and another participant did not continue in the extension after 104 weeks. ‡Not considered related to study treatment.

WOMAC-A

- Least squares mean (LSM) improvements from baseline among the 3 doses were observed for WOMAC-A pain scores in both the not pretreated group (range of reduction across doses, 2.3-2.6 points [36%-38%]) and corticosteroid pretreated group (range of reduction across doses, 3.4-3.6 points [51%-53%]; Figure 3, top panel)
- When stratified by K-L grade, LSM improvements in WOMAC-A pain scores were observed through Week 156 for all subgroups excluding K-L grade 4 in the not pretreated group (Figure 3, bottom panel)

Figure 3. LSM change from baseline in WOMAC-A pain scores.

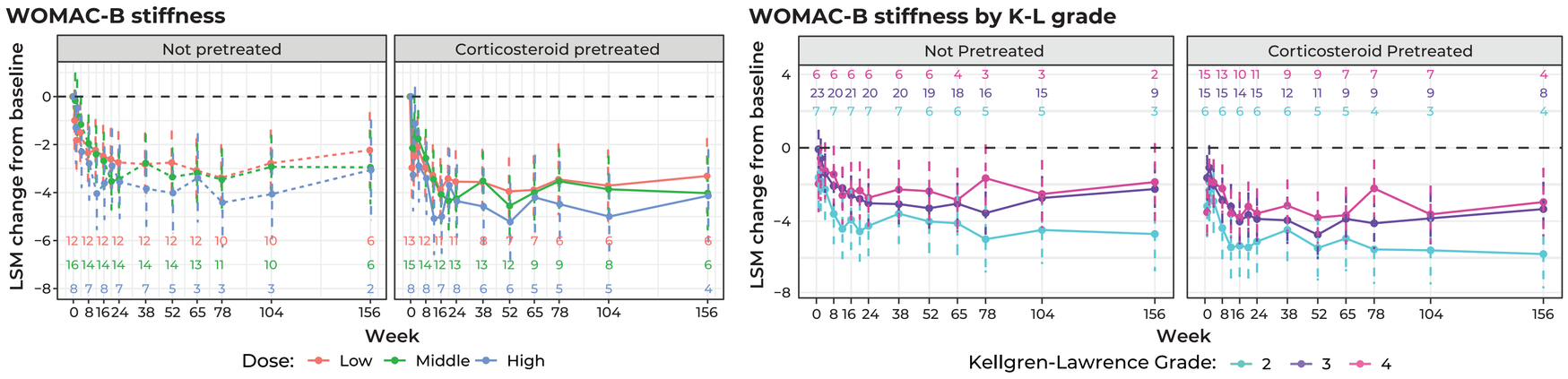


Values in color are the sample size over time by dose or K-L grade. K-L, Kellgren-Lawrence; LSM, least squares mean; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

WOMAC-B

- LSM improvements from baseline among the 3 doses were observed for WOMAC-B stiffness scores in both the not pretreated group (range of reduction across doses, 2.2-3.1 points [28.5%-40.5%]) and corticosteroid pretreated group (range of reduction across doses, 3.3-4.1 points [51%-63%]; Figure 4, top panel)
- When stratified by K-L grade, LSM improvements in WOMAC-B stiffness scores were observed through Week 156 for all subgroups excluding K-L grade 4 in the not pretreated group (Figure 4, bottom panel)

Figure 4. LSM change from baseline in WOMAC-B stiffness scores.

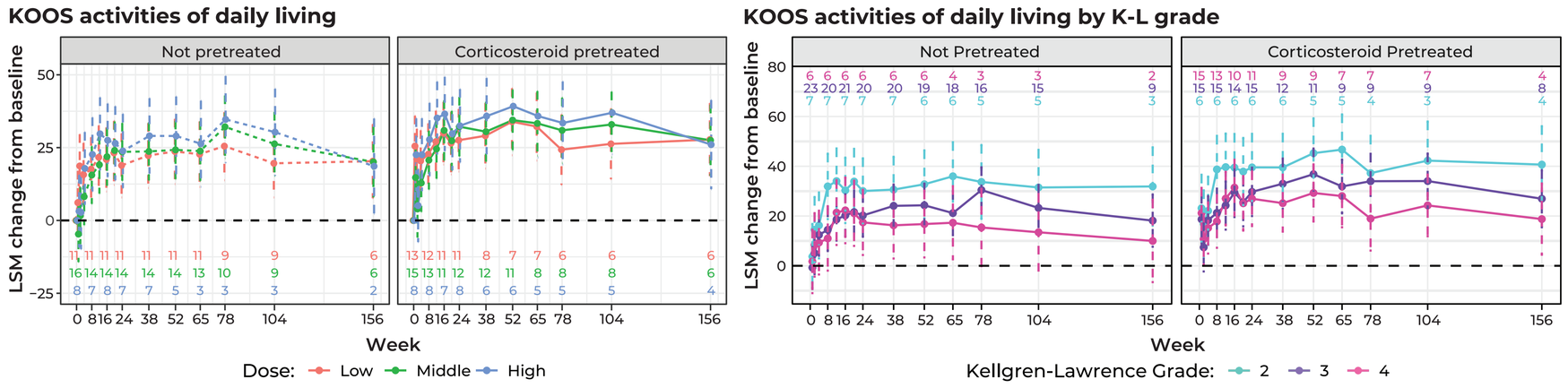


Values in color are the sample size over time by dose or K-L grade. K-L, Kellgren-Lawrence; LSM, least squares mean; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

KNEE INJURY AND OSTEOARTHRITIS OUTCOME SCORE

- LSM improvements in Knee Injury and Osteoarthritis Outcome Score (KOOS) activities of daily living (shown as increase from baseline) stratified by dose (Figure 5, top panel) and K-L grade (Figure 5, bottom panel) were observed at all doses and grades excluding K-L grade 4 in the not pretreated group

Figure 5. LSM change from baseline in KOOS activities of daily living through week 156.



Values in color are the sample size over time by dose or K-L grade. K-L, Kellgren-Lawrence; LSM, least squares mean; KOOS, Knee Injury and Osteoarthritis Outcome Score.

SAFETY

- No serious treatment-emergent adverse events related to the treatment or procedure were reported regardless of corticosteroid pretreatment or dose level
- New or worsening treatment-related knee effusions were the most common adverse event
  - In the not pretreated group, 61% of participants (22/36) experienced a total of 23 treatment-related knee effusions; 22% (5/23), 61% (14/23), and 17% (4/23) were mild (grade 1), moderate (grade 2), and severe (grade 3), respectively
    - Treatment-related effusion events began within a median of 3 days (range, 0-56 days) after PCRX-201 administration and resolved in a median of 18 days (range, 2-165 days)
  - In the corticosteroid pretreated group, 36% of participants (13/36) experienced a total of 14 treatment-related effusion events; 7% (1/14), 86% (12/14), and 7% (1/14) were mild (grade 1), moderate (grade 2), and severe (grade 3), respectively
    - Treatment-related effusion events began within a median of 9.5 days (range, 1-30 days) after PCRX-201 administration and resolved in a median of 33 days (range, 3-111 days)
- No additional dose-related index knee effusions were reported between 104 and 156 weeks in either group
- The percentage of participants with treatment-related knee effusions was similar across subgroups stratified by K-L grade (K-L grade 2, 54%; K-L grade 3, 45%; K-L grade 4, 52%)

DISCLOSURES: PGC is a consultant for Alfasigma, Eupraxia Pharmaceuticals, Formation Bio, Galapagos, Genascence, Grünenthal, GSK, Janssen, Levicept, Eli Lilly and Company, MEDIPOST, Moebius Medical, Novartis, Orion Pharma, Pacira BioSciences, Inc., Stryker, and Takeda Pharmaceuticals; has received speaker/honoraria (includes speakers bureau, symposia, and expert witness) from AbbVie, Eli Lilly and Company, Novartis, and Sandoz. **AM** is a consultant for ACI, Ampio Pharmaceuticals, Aptissen, Apos Health, Bruder Consulting and Venture Group, Chiron, Chondropeptix, Contura, Enlivex, Grünenthal, HALEON, Hypera Pharma, ICM (South Korea), Kangstem (South Korea), Kolon Life Science (South Korea), Kolon TissueGene, Laboratoires Expanscience, Nestlé Health Science, Opella, Pacira BioSciences, Inc., Pluri, Sanofi, Sunac Therapeutics, Synartro, SynOA Therapeutics, and Viatris and has received research support from Research Council of Lithuania/Lietuvos mokslo taryba, Research Council of Finland/Suomen Akatemia, and the European Commission. **SC** is a consultant for Amgen and has received grant/research support from Pacira BioSciences, Inc.

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