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Improvements in Pain, Stiffness, and Function After a Single Intraarticular Injection of Gene Therapy PCRX-201 for Knee Osteoarthritis: a Subgroup Analysis by Structural Severity

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OBJECTIVE

The objective of this post hoc subgroup analysis was to assess the impact of PCRX-201 gene therapy on pain, stiffness, and function in patients with osteoarthritis of the knee (OAK) stratified by structural severity (assessed by Kellgren/Lawrence [K/L] grade)

CONCLUSIONS

1. A single IA injection of PCRX-201 led to improvements in pain, stiffness, and function for up to 104 weeks in all structural severity subgroups
2. The greatest improvements were observed in individuals with K/L grade of 2; improvements were also observed for those with K/L grade of 3 or 4, suggesting that PCRX-201 may be useful across the spectrum of OAK severity
3. These data warrant further investigation in an ongoing randomized, double-blind, active-controlled phase 2 study (NCT06884865)

INTRODUCTION

- There is an unmet need for developing safe and effective treatments for OAK that provide long-term improvements in pain and function as current treatments provide only short-term relief[1]
  - There is a particular unmet need for treatment options for patients with moderate-to-severe OAK (K/L grade of 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 intraarticular (IA) injection; after 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 promotor that is only active when local inflammation is present in the target knee and mimics 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 104 weeks

METHODS

- This open-label phase 1 trial (NCT04119687) enrolled 2 cohorts who received ultrasound-guided IA injection of PCRX-201 (Figure 1)
  - Cohort 1 received PCRX-201 at 1 of 3 doses (low, middle, or high; n=36)
  - Cohort 2 received pretreatment with IA methylprednisolone 40 mg immediately before PCRX-201 administration at the same doses to maximize vector tolerability and transduction as well as explore the benefit of immune modulation (n=36)
- The current post hoc analysis has a median follow-up of 104 weeks and examines results by K/L grade

Figure 1. Study design.

Inclusion criteria

Adults aged 30-80 years with moderate-to-severe OAK
- K/L 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
PCRX-201 IA ultrasound-guided injection

Cohort 2: corticosteroid pretreated
IA methylprednisolone 40 mg immediately before PCRX-201 IA ultrasound-guided injection

Endpoints and assessments to 104 weeks

Primary endpoint: safety assessments (AEs, TEAEs; graded per CTCAE version 5.0), repeated index knee assessments, laboratory evaluations

Exploratory Efficacy Outcomes: WOMAC pain (WOMAC-A) and stiffness (WOMAC-B) subscales; KOOS pain, symptoms, activities of daily living, sport and recreation function, and knee-related quality of life

AE, adverse event; GC, genome copies; IA, intraarticular; K/L, Kellgren/Lawrence; KOOS, Knee Injury and Osteoarthritis Outcome Score; MRI, magnetic resonance imaging; NAb, neutralizing antibody; NSRI, nonselective serotonin reuptake inhibitor; OAK, osteoarthritis of the knee; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TEAE, treatment-emergent AE; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

RESULTS

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

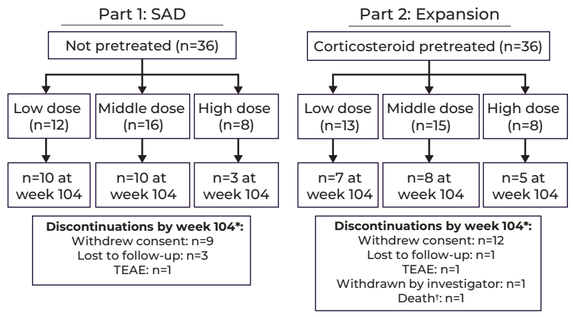
- Overall, 36 participants were enrolled and treated in each cohort (Figure 2)
- Participant demographics and baseline characteristics were similar across cohorts (Table)
- There were a similar number of discontinuations by week 104 in both groups (Figure 2)

Table. Participant Demographics and Baseline Characteristics

	Not pretreated cohort (n=36)	Corticosteroid 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)
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 pain score, mean (SD)	6.4 (1.0)	6.8 (1.0)
Follow-up, median (range), wk	104 (15-104)	104 (8-104)

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 104 after providing data; in those cases, data at week 104 are included in the analysis. †Not considered related to study treatment.

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% (22/36) of participants 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% (13/36) of participants 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)

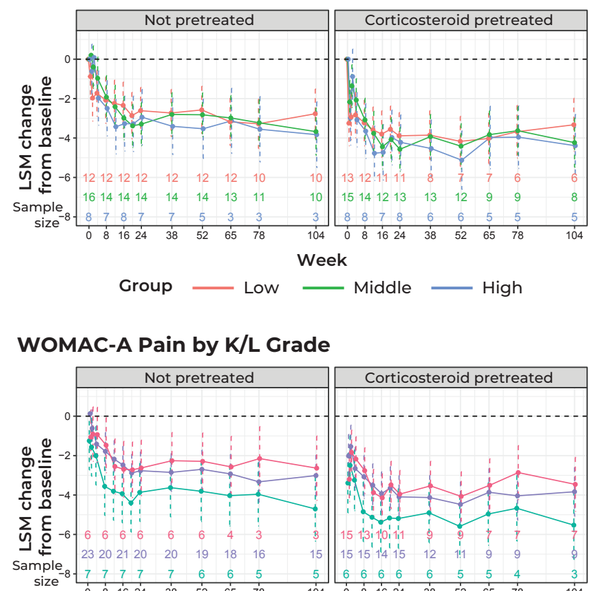
SAFETY (CONTINUED)

- 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%; grade 4 K/L, 52%)

WOMAC-A

- Least squares mean (LSM) improvements from baseline among the 3 dose groups were observed for WOMAC-A pain scores in both the not pretreated cohort (range, 2.8-3.8–point [41%-58%] reduction) and corticosteroid pretreated cohort (range, 3.3-4.4–point [48%-65%] reduction; Figure 3, top panel)
- When stratified by K/L grade, LSM improvements in WOMAC-A pain scores were observed for all subgroups (Figure 3, bottom panel)

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

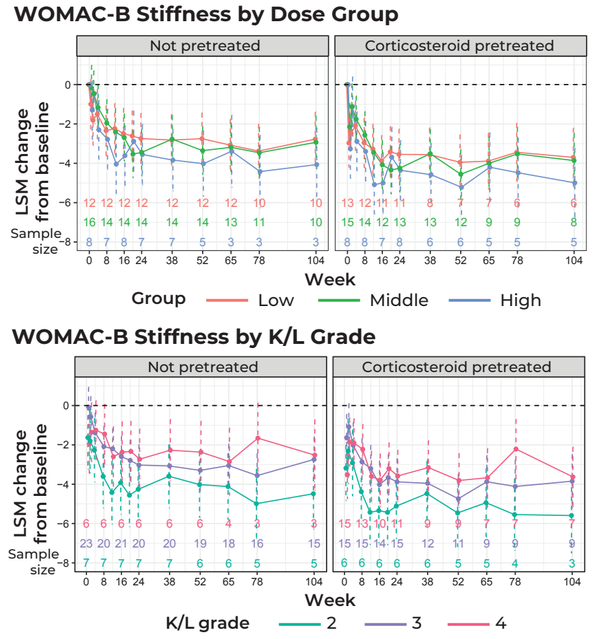


K/L, Kellgren/Lawrence; LSM, least squares mean; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

WOMAC-B

- LSM improvements among the 3 dose groups were observed for WOMAC-B stiffness scores in the not pretreated cohort (range, 2.8-4.1–point [33%-53%] reduction) and corticosteroid pretreated cohort (range, 3.7-5.0–point [53%-72%] reduction; Figure 4, top panel)
- When stratified by K/L grade, LSM improvements were observed in WOMAC-B stiffness scores in all subgroups (Figure 4, bottom panel)

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

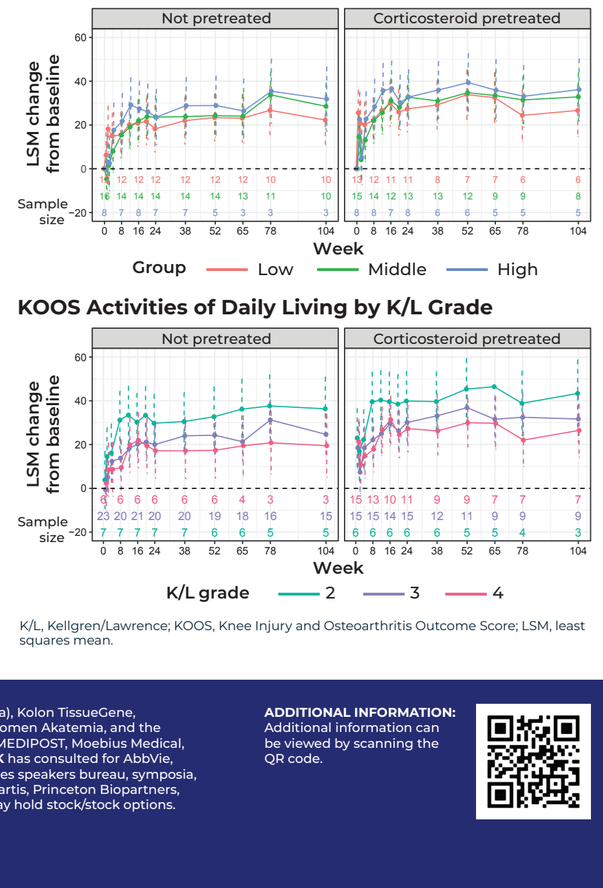


K/L, Kellgren/Lawrence; LSM, least squares mean; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

KNEE INJURY AND OSTEOARTHRITIS OUTCOME SCORE (KOOS)

- LSM improvements in KOOS activities of daily living score (shown as increase from baseline) stratified by dose (Figure 5, top panel) and K/L grade (Figure 5, bottom panel) were observed at all grades

Figure 5. LSM change from baseline for KOOS activities of daily living scores.



K/L, Kellgren/Lawrence; KOOS, Knee Injury and Osteoarthritis Outcome Score; LSM, least squares mean.

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ADDITIONAL INFORMATION: Additional information can be viewed by scanning the QR code.

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IMPROVEMENTS IN PAIN, STIFFNESS, AND FUNCTION AFTER A SINGLE INTRAARTICULAR INJECTION OF GENE THERAPY PCRX-201 FOR KNEE OSTEOARTHRITIS: A SUBGROUP ANALYSIS BY STRUCTURAL SEVERITY

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Participant Demographics and Baseline Characteristics

- Participant demographics and baseline characteristics were similar across cohorts
  - Most participants were women with a K/L grade of 3-4, the mean WOMAC pain score was similar in both cohorts, and ~75% of participants had bilateral OAK

Participant Demographics and Baseline Characteristics		
	Not pretreated cohort (n=36)	**Corticosteroid 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)
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 pain score, mean (SD)	6.4 (1.0)	6.8 (1.0)
Follow-up, median (range), wk	104 (15-104)	104 (8-104)
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)

BMI, body mass index; IQR, interquartile range; K/L, Kellgren/Lawrence; OAK, osteoarthritis of the knee; SD, standard deviation; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

WOMAC-A Pain Scores and WOMAC-B Stiffness Scores Stratified by K/L Grade

- When stratified by K/L grade, LSM improvements were observed in WOMAC-A pain scores and WOMAC-B stiffness scores in all subgroups

LSM Improvements in WOMAC-A Pain Scores and WOMAC-B Stiffness Scores at Week 104 Stratified by K/L Grade

K/L grade	Not pretreated: point reduction (%)	n	Corticosteroid pretreated: point reduction (%)	n
WOMAC-A Pain				
2	4.7 (70.5)	5	5.5 (81)	3
3	3.0 (45.1)	15	3.8 (55)	9
4	2.6 (42.5)	3	3.5 (53)	7
WOMAC-B Stiffness				
2	4.5 (49)	5	5.6 (70)	3
3	2.7 (35)	15	3.8 (56)	9
4	2.5 (35)	3	3.6 (56)	7

K/L, Kellgren/Lawrence; LSM, least squares mean; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

KOOS Activities of Daily Living Score Stratified by K/L Grade

- When stratified by K/L grade, LSM improvements were observed in KOOS activities of daily living score in all subgroups

LSM Improvements in KOOS Scores at Week 104 Stratified by K/L Grade

K/L grade	Not pretreated: point increase	n	Corticosteroid pretreated: point increase	n
2	36.3	5	43.3	3
3	24.7	15	31.7	9
4	19.5	3	26.5	7

K/L, Kellgren/Lawrence; KOOS, Knee Injury and Osteoarthritis Outcome Score; LSM, least squares mean.