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Safety and Preliminary Efficacy of PCRX201, an Intraarticular Gene Therapy for Knee Osteoarthritis: a Phase 1, Open-label, Single Ascending Dose Study

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OBJECTIVE

To report preliminary safety and efficacy results of PCRX201 from a phase 1 study in knee osteoarthritis (OA)

CONCLUSIONS

1. PCRX201 was generally well tolerated, with the main treatment-related adverse event (TRAE) being index knee effusion, which generally resolved in a matter of weeks with conservative care or intraarticular steroids
   - There were no treatment-related severe AEs, deaths, or late recurrences and no unusual patterns of nonrelated AEs during follow-up
   - A decreased frequency of overall and grade 3 index knee events was observed in the steroid-pretreated cohort compared with the not pretreated cohort
2. Improvements in knee pain were observed across all dose groups and cohorts receiving PCRX201; pretreatment with steroids did not appear to affect transduction of PCRX201
3. Preliminary results from this phase 1 open-label study of PCRX201 are promising and support further investigation of PCRX201 for knee OA
   - This study is ongoing, and participants will be followed for 5 years

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REFERENCES: 1. Onishi K et al. *Crit Rev Phys Rehabil Med.* 2012;24(3-4):251-264. **2.** Senter R et al. *Hum Gene Ther.* 2022;33(9-10):541-549.

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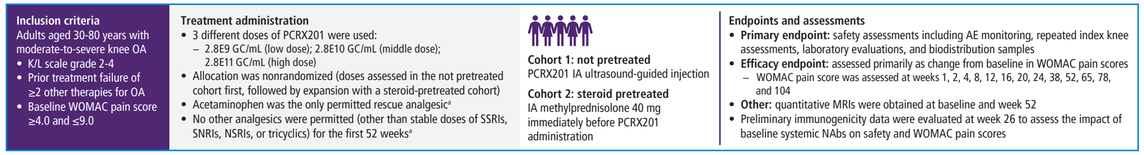
INTRODUCTION

- OA, the most common joint disorder in the world, causes chronic pain and inflammation in the affected joint, which ultimately diminishes quality of life[1]
  - Interleukin 1 (IL-1) is believed to be an important driver of inflammation, pain, and disease progression in OA[2]
- PCRX201 is a novel helper-dependent adenovirus that locally expresses the human IL-1 receptor antagonist (IL-1Ra) gene and is designed to be activated by a nuclear factor κB–responsive promoter during inflammation to reflect a natural response[2]
  - IL-1Ra competitively blocks binding of both IL-1α and IL-1β but has no inherent signaling capabilities itself[2]
  - A preliminary study in an anterior cruciate ligament transfection rat model of OA found that a rat surrogate of PCRX201 mitigated OA-related joint damage and remained localized to the joint space, with a tolerable safety profile[2]

METHODS

- This proof-of-concept, open-label, single ascending dose study (NCT04119687) enrolled 2 cohorts (Figure 1)

Figure 1. Study design.



AE, adverse event; GC, genome copies; IA, intraarticular; K/L, Kellgren/Lawrence; MRI, magnetic resonance imaging; NAb, neutralizing antibody; 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. [a]Nonsteroidal anti-inflammatory drugs were allowed at the discretion of the investigator after day 60.

RESULTS

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

- 72 participants were enrolled between March 2020 and December 2021
  - Low-, middle-, and high-dose PCRX201 was administered to 12, 16, and 8 participants, respectively, in the not pretreated cohort (n=36) and to 13, 15, and 8 participants, respectively, in the steroid-pretreated cohort (n=36)
- Median follow-up was 64.9 (range, 15.1-106.1) weeks in the not pretreated cohort and 37.6 (range, 7.6-52.0) weeks in the steroid-pretreated cohort
  - At data cutoff (July 2022), 13 participants (36%) in the not pretreated cohort and 11 participants (31%) in the steroid-pretreated cohort had discontinued
- Participant demographics and baseline characteristics are shown in Table 1

Table 1. Demographics and Baseline Characteristics

	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)
Sex, n (%)		
Male	15 (41.7)	15 (41.7)
Female	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)
Race, n (%)		
Asian	1 (2.8)	0
Black or African American	4 (11.1)	4 (11.1)
White	31 (86.1)	32 (88.9)
BMI, mean (SD), kg/m^2	32.1 (4.2)	31.2 (4.9)
Years since primary diagnosis, mean (SD)	8.7 (8.8)	14.6 (10.9)
Unilateral or bilateral, 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; SD, standard deviation; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

SAFETY

- Decreased frequency and severity of index knee effusions were observed in the steroid-pretreated cohort compared with the not pretreated cohort (Table 2)
  - 93.2% of knee-related effusion TRAEs resolved with rest, ice, acetaminophen, or aspiration of synovial fluid
  - All grade 3 knee-related effusion AEs resolved with intraarticular steroids

Table 2. Treatment-Related Index Knee Effusions

	Not pretreated cohort (n=36)	Steroid-pretreated cohort (n=36)
Knee effusion, n/N (%)		
Low dose	6/12 (50)	4/13 (31)
Middle dose	9/16 (56)	4/15 (27)
High dose	8/8 (100)	5/8 (63)
Severity of knee effusion, n/N (%)[a]		
Grade 1	6/23 (26)	1/13 (8)
Grade 2	12/23 (52)	11/13 (92)
Grade 3	5/23 (22)	1/13 (8)

[a]Severity determined by the principal investigator using medical judgment and general guidelines from Common Terminology Criteria for Adverse Events version 5.0.

- Rates of other TRAEs were similar between cohorts (Table 3)
  - The most common TRAEs other than knee effusions were self-limited chills and concurrent headache

Table 3. Other TRAEs

	Not pretreated cohort (n=36)	Steroid-pretreated cohort (n=36)
Self-limited chills, n/N (%)		
High dose	2/36 (6)	1/36 (3)
Concurrent headache, n/N (%)		
Low dose	-	1/36 (3)
High dose	2/36 (6)	1/36 (3)
Flu-like symptoms, n/N (%)		
High dose	-	1/36 (3)
Self-limited fever, n/N (%)[a]		
Middle dose	-	1/36 (3)
Severe injection pain, n/N (%)[b]		
Middle dose	-	1/36 (3)

TRAE, treatment-related adverse event. [a]Fever at onset of knee AE. [b]Resulted in early termination of injection with no related knee AEs.

IMMUNOGENICITY

- From an initial sample set from the not pretreated cohort (13 participants, including 5 at low dose and 8 at middle dose), systemic baseline neutralizing antibody (NAb) positivity did not appear to notably affect risk of knee-related AEs or Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain response (Tables 4 and 5)

Table 4. Systemic NAb Positivity at Baseline Versus Knee-Related AEs

Systemic NAb	Index knee-related AE	No index knee-related AE
Positive, n	2	5
Negative, n	4	2

AE, adverse event; NAb, neutralizing antibody.

Table 5. Systemic NAb Positivity at Baseline Versus WOMAC Pain Response

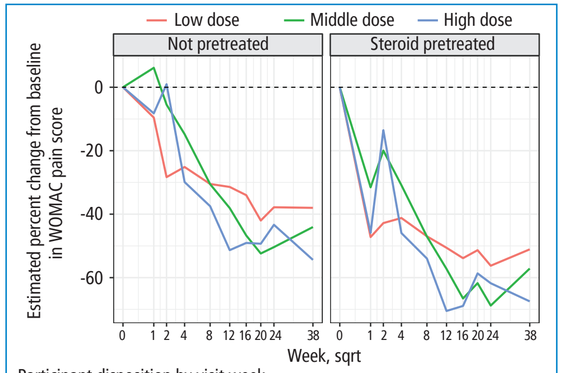
Systemic NAb	Any substantial pain response[a]	No substantial pain response[a]
Positive, n	3	4
Negative, n	4	2

AE, adverse event; NAb, neutralizing antibody; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index. [a]Substantial pain response defined as 50% reduction in WOMAC pain score from baseline.

EFFICACY: PAIN SCORES

- Improvements in knee pain were observed across all dose groups and treatment cohorts receiving PCRX201 (Figure 2)
  - Pretreatment with steroids did not appear to impact PCRX201 transduction

Figure 2. Change in WOMAC pain score from baseline by dose group and treatment cohort and participant disposition by visit week.



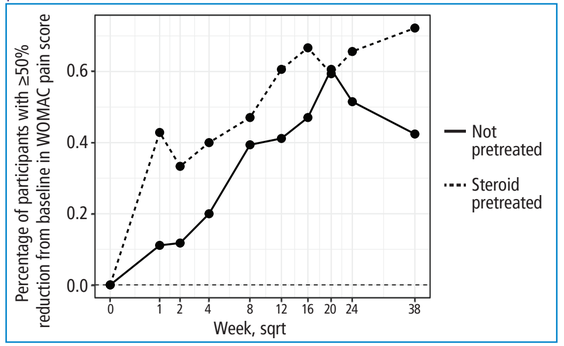
Participant disposition by visit week

Cohort	Dose	0	1	2	4	8	12	16	20	24	38
Not pretreated	Low dose	12	12	12	12	12	12	12	12	12	12
Not pretreated	Middle dose	16	16	15	15	14	14	14	14	14	14
Not pretreated	High dose	8	8	7	8	7	8	8	7	7	7
Steroid pretreated	Low dose	13	13	13	12	12	12	11	11	11	5
Steroid pretreated	Middle dose	15	14	15	15	14	13	12	13	13	9
Steroid pretreated	High dose	8	8	8	8	8	8	7	8	8	4

Covariates in the model include cohort, steroid pretreatment, all visits up to week 38, cohort by visit interaction, pretreatment by visit interaction, and participant variability (as a random intercept). sqrt, square root; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

- Preliminary efficacy results suggested substantial improvement in pain across PCRX201 cohorts (Figure 3)

Figure 3. Percentage of participants with ≥50% reduction from baseline in WOMAC pain score.



Preliminary results of observed data, with no imputations of missing values; data are reported through up to 6 months after treatment administration in the last participant. sqrt, square root; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.