LB-47

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

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OBJECTIVE

To investigate the safety and efficacy of a single intraarticular (IA) injection of PCRX-201 in participants with moderate-to-severe osteoarthritis of the knee (OAK) in a phase 1 trial

CONCLUSIONS

1. A single IA injection of PCRX-201 had an acceptable safety profile with sustained clinical effects at all dose levels across the 100-fold dose range examined to date for up to 52 weeks after injection as assessed with patient-reported outcomes
2. The steroid pretreated group appeared to have fewer joint effusion events and more pain reduction than the not pretreated group, suggesting steroid pretreatment may have a favorable impact on efficacy
3. Baseline NAbs did not appear to affect either the incidence of treatment-emergent adverse events (TEAEs) or the reduction in WOMAC pain and stiffness from PCRX-201
4. There was not a strong dose-response relationship, suggesting the lowest dose of PCRX-201 used may be sufficient in future clinical studies
5. Additional disease modification data are forthcoming as longer-term data become available
6. These promising results support the further investigation of PCRX-201 with steroid pretreatment in participants with OAK, which is planned in future clinical studies

INTRODUCTION

- Preclinical and clinical studies provide support for targeting interleukin-1 (IL-1) to improve both pain and function and slow disease progression, given the lack of durable symptomatic relief options for patients with OAK[1-3]
- PCRX-201 is an investigational helper-dependent, nonintegrating, nonreplicating adenovirus serotype 5 vector for IA injection[1]
  - PCRX-201 expresses IL-1 receptor antagonist (IL-1Ra), an inhibitor of IL-1 signaling, under control of a NF-κB inducible promotor[1]
- Gene therapy approaches such as PCRX-201 require specific considerations for participant selection, administration, and trial design, such as the following:
  - Pretreatment with IA corticosteroids to enhance gene transfer[4,5]
  - Selection of the inducible promoter may reduce the risk of gene silencing over time[6]
  - Assessment of the impact of NAbs on gene transfer[7,8]
  - Evaluation of the durability of the response[9]

METHODS

- This open-label phase 1 trial (NCT04119687) enrolled 2 cohorts: "not pretreated" and "steroid pretreated" with IA methylprednisolone 40 mg immediately before PCRX-201 ultrasound-guided administration
  - PCRX-201 doses: Low, 2.8E9 GC/mL; Middle, 2.8E10 GC/mL; High, 2.8E11 GC/mL
- Inclusion criteria: adults with OAK, baseline WOMAC pain score ≥4.0 and ≤9.0 of 10.0, Kellgren-Lawrence (K/L) grade 2-4, prior treatment failure of ≥2 other OA therapies
- Endpoints: primary, safety assessments; efficacy included WOMAC, KOOS, and effects of NAbs

RESULTS

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

- Similar across cohorts: most participants were female with a K/L grade of 3-4, the mean WOMAC pain score was 6.8 in both cohorts, and ~75% of participants had bilateral OAK
- The median follow-up for this data cut was 52 (range, 17-52) weeks in the not pretreated cohort and 52 (range, 10-52) weeks in the steroid pretreated cohort
- By week 52, 8 participants discontinued from cohort 1 (4 withdrew consent, 3 lost to follow-up, and 1 TEAE), and 12 discontinued from cohort 2 (8 withdrew consent, 1 lost to follow-up, 1 TEAE, 1 withdrawn by investigator, and 1 death [death was not considered related to the study treatment])

SAFETY

- No serious adverse events related to the treatment or procedure were reported regardless of steroid pretreatment or dose level (Table)
- Effusion occurred more frequently in the not pretreated cohort than the steroid pretreated cohort
  - Not pretreated cohort: events began within 56 days of administration and resolved in a median of 18 (range, 2-165) days
  - Steroid pretreated cohort: events began within 30 days of administration and resolved in a median of 33 (range, 3-111) days

EFFICACY

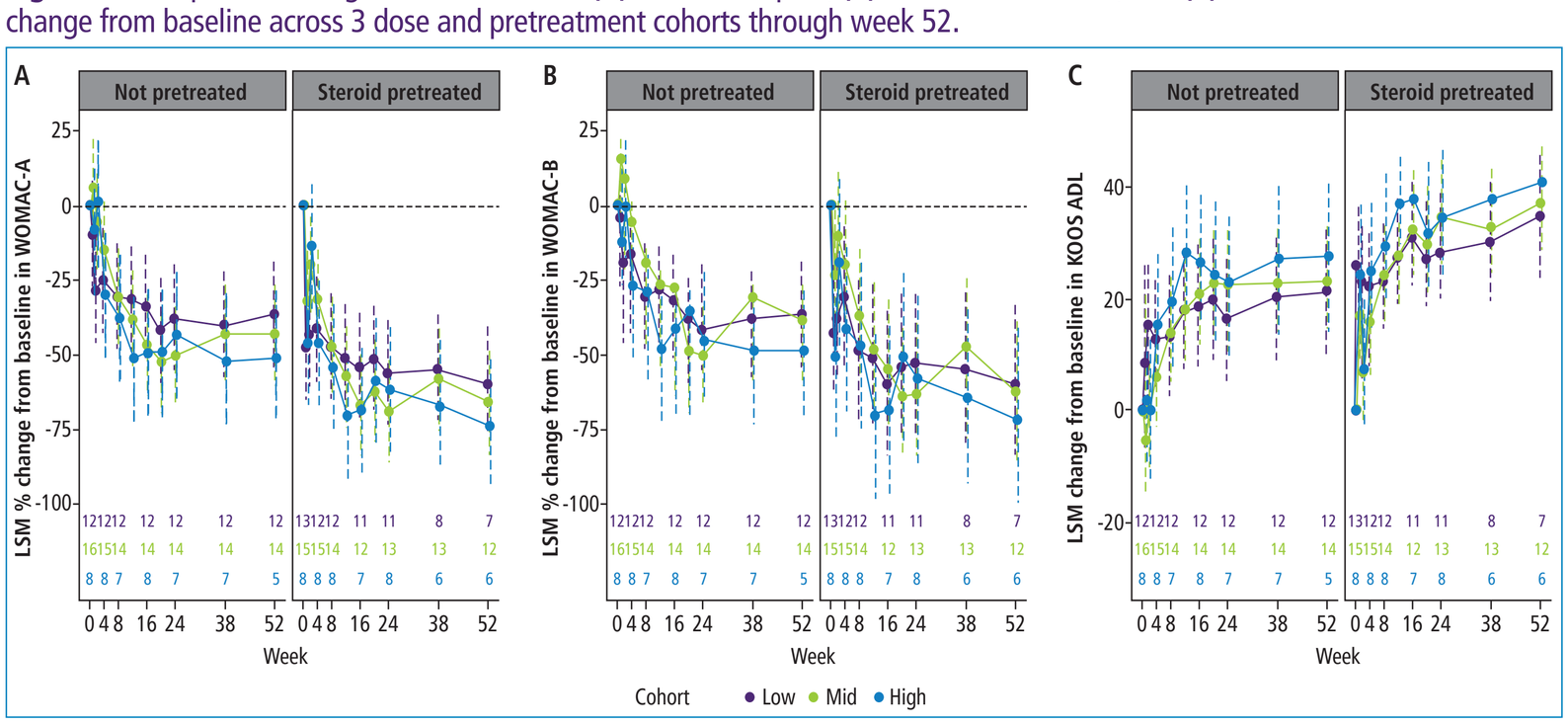
- Improvement from baseline in the WOMAC-A pain subscale was reported across dose levels and cohorts by week 8; at week 52, the least squares mean (LSM) percent change (standard error of the mean [SEM]) from baseline across doses ranged from –51.3% (11.7%) to –36.8% (9.3%) for the not pretreated cohort, with a greater magnitude of reduction (–74.2% [11.5%] to –59.7% [9.8%]) observed for the steroid pretreated cohort (Figure 1)
  - Importantly, joint effusion did not negatively affect WOMAC pain response
- The LSM (SEM) percent change from baseline across doses on the WOMAC-B stiffness subscale ranged from –49.0% (16.0%) to –36.6% (12.4%) for the not pretreated and from –72.5% (15.6%) to –60.0% (13.5%) for the steroid pretreated cohorts
- Favorable improvements were observed in knee function and were greater in the steroid pretreated cohort as assessed by KOOS activities of daily living scores (Figure 1)
- Baseline NAb positivity ranged from 13% to 64% across dose levels and cohorts; however, the presence of baseline NAbs did not impact WOMAC-A pain scores (Figure 2), WOMAC-B stiffness scores, or incidence of effusions (data not shown)

Table. Summary of TEAEs[a,b]

	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	9 (75.0)	15 (93.8)	8 (100)	32 (88.9)	11 (84.6)	13 (86.7)	8 (100.0)	32 (88.9)
SAE	0	1 (6.3)	1 (12.5)	2 (5.6)	1 (7.7)	1 (6.7)	2 (25.0)	4 (11.1)
TEAE grade ≥3	1 (8.3)	3 (18.8)	3 (37.5)	7 (19.4)	2 (15.4)	3 (20.0)	2 (25.0)	7 (19.4)
TEAE occurring in ≥10% of participants in either cohort								
Joint effusion	6 (50.0)	10 (62.5)	8 (100.0)	24 (66.7)	5 (38.5)	5 (33.3)	5 (62.5)	15 (41.7)
Arthralgia	5 (41.7)	3 (18.8)	1 (12.5)	9 (25.0)	4 (30.8)	6 (40.0)	6 (75.0)	16 (44.4)
Joint swelling	6 (50.0)	1 (6.3)	1 (12.5)	8 (22.2)	0	2 (13.3)	0	2 (5.6)
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)
Musculoskeletal pain	0	0	0	0	2 (15.4)	0	2 (25.0)	4 (11.1)

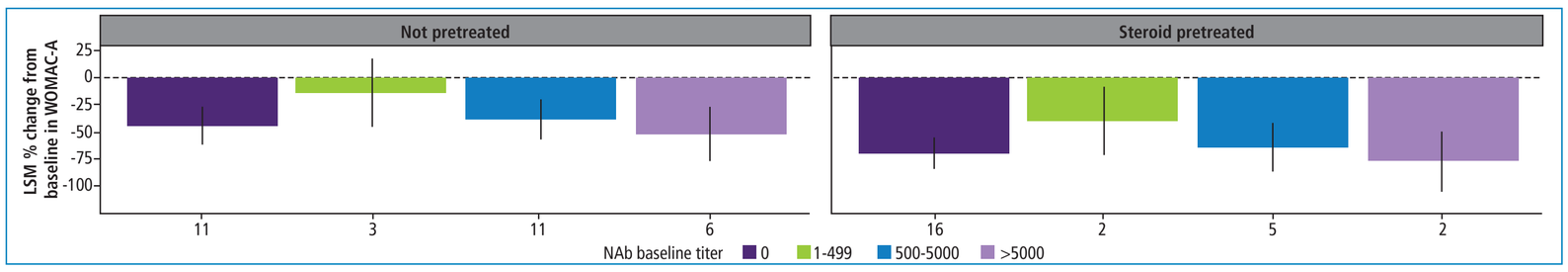
[a]Including all TEAEs related and unrelated to treatment. [b]AE grading was performed according to CTCAE v5.0. SAE, serious adverse event.

Figure 1. LSM percent change from baseline for **(A)** WOMAC-A pain, **(B)** WOMAC-B stiffness, and **(C)** KOOS ADL score LSM change from baseline across 3 dose and pretreatment cohorts through week 52.



Data are as observed. ADL, activities of daily living.

Figure 2. Impact of baseline serum NAb titer on percent change from baseline in WOMAC-A pain score at 52 weeks.



The number of participants at each time point is indicated below each graph bar.

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

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