

Sustained Clinical Efficacy and Safety at 3 Years After Intraarticular PCRX-201 Gene Therapy in Patients With Knee Osteoarthritis

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OBJECTIVE

To assess the impact of PCRX-201 on pain, stiffness, function, and immunogenicity in patients with knee osteoarthritis (OA) after 156 weeks

CONCLUSIONS

- 1 A single intraarticular (IA) injection of PCRX-201 after glucocorticoid pretreatment in patients with knee OA had an acceptable safety profile and sustained clinical efficacy for up to 156 weeks
- 2 Preexisting neutralizing antibodies did not affect PCRX-201 efficacy or safety at all 3 doses
- 3 Glucocorticoid pretreatment demonstrated greater improvement in clinical scores than no pretreatment
- 4 These results support the ongoing phase 2 study strategy of PCRX-201 using glucocorticoid pretreatment and a 1.4×10^{10} viral genome copies (GC) dose or a 1.4×10^{11} viral GC dose



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DISCLOSURES: **SC** has received consulting fees from Liford, Pacira BioSciences, AbbVie, Lilly, Pfizer, Spyre, and UCB and holds stock or stock options in Liford. **PGC** has received consulting fees from AbbVie, Alfasigma, Lilly, Eupraxia, Formation Bio, Genasense, Grunenthal, Kolon TissueGene, Levecept, Moebius, Novartis, Orion, Pacira BioSciences, Stryker, and Takeda. **MCH** has received consulting fees from Pacira BioSciences and holds stock or stock options in Regenosine and Theralogix. **AK** has received consulting fees from AbbVie, Allinbio, Aurinia, Bristol Myers Squibb, Covati, Econ, Gilead, Genzyme, Grunenthal, GSK, Haila, Horizon, Innovaderm, Janssen, Moonlake, Novartis, Pacira BioSciences, Prometheus, Sanofi, Santa Ana Bio, Synact, Takeda, UCB, VYNE, XBiotech, and Xencon; received paid speaker fees from AbbVie, Clinical Viewpoints, Excel Continuing Education, GSK, Lilly, Pfizer, Prime, Sanofi, Regeneron, UCB, and YuMedia; participated in advisory boards for Janssen, Tonix, and UCBs and holds stock or stock options in Pfizer, GSK, Gilead, Novartis, and Amgen. **WR, MK, NJ, SJ, MD, JS, and DJ** are employees of Pacira BioSciences, and may hold stock or stock options in the company.
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REFERENCES: 1. Deshpande et al. *Arthritis Care Res (Hoboken)*. 2016;68(12):1743-1750. 2. Buelt, Narducci. *Am Fam Physician*. 2021;103(2):120-121. 3. Li et al. *Int J Mol Sci*. 2023;24(9):7736. 4. Senter et al. *Hum Gene Ther*. 2022;33(9-10):541-549.

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INTRODUCTION

- Knee OA is a common disease affecting ~15 million people in the United States¹
- There is an urgent unmet need for additional treatments in knee OA because current treatments provide only short-term pain relief and are often associated with adverse effects and contraindications²
- Gene therapy using viral vectors has the potential to treat many diseases³
- PCRX-201 (enekinragene inzadenovec) is a novel high-capacity adenovirus (HCAd) serotype 5 vector carrying a transgene encoding for the inflammation-inducible expression of interleukin-1 receptor antagonist (IL-1Ra) and is under investigation to treat knee OA via IA injection⁴
- This open-label phase 1 trial (NCT0419687) investigated the safety and efficacy of PCRX-201, with ongoing long-term follow-up

RESULTS

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

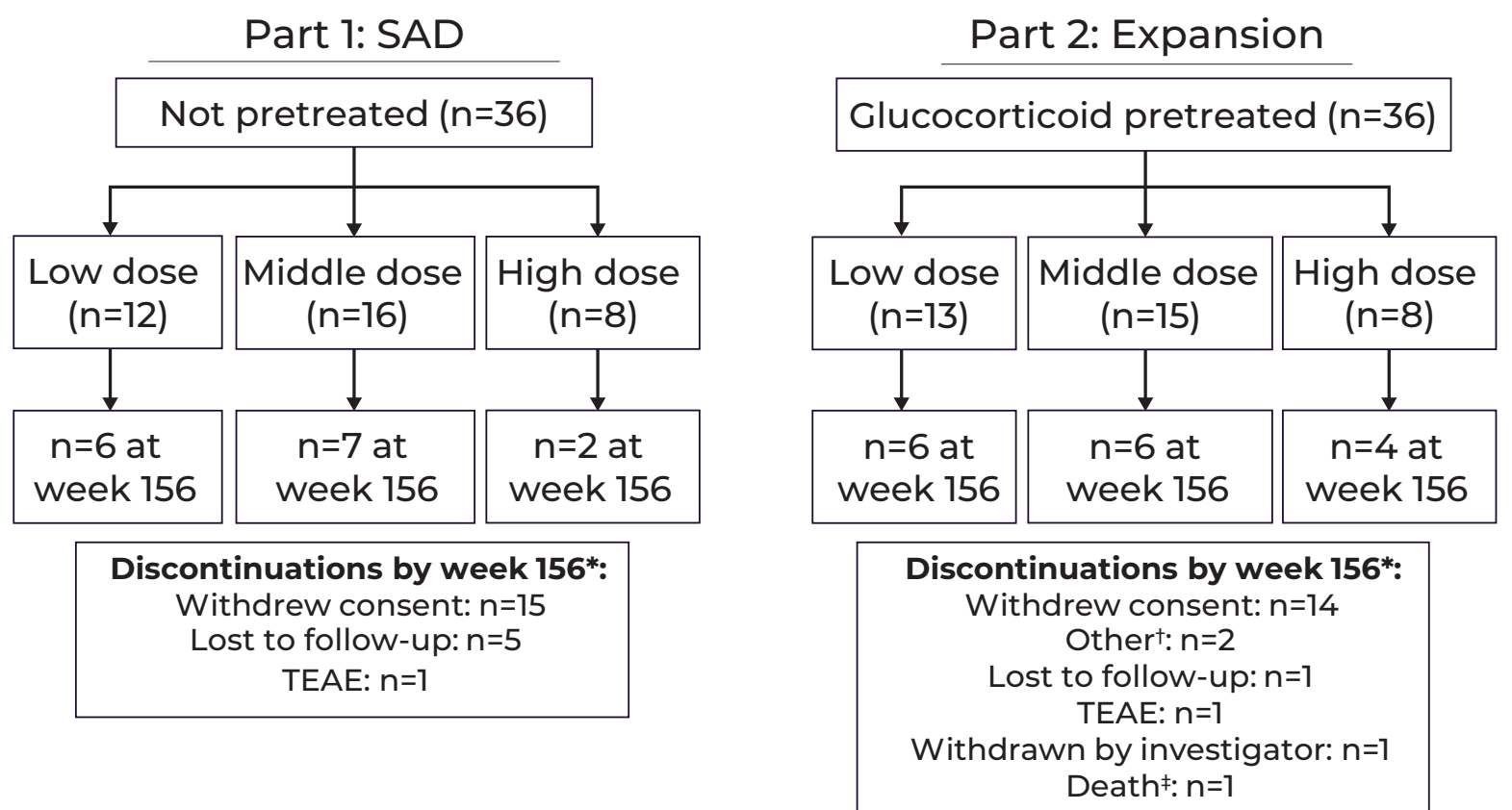
- 36 participants were enrolled and treated in each group (Figure 2)
- Participant demographics and baseline characteristics were similar across groups (Table 1)
 - Most participants were women (58%) with a Kellgren-Lawrence grade of 3 or 4 (81% in the not pretreated group and 83% in the glucocorticoid pretreated group)
 - WOMAC-A pain score was similar in both groups, and ~75% of participants had bilateral knee OA
- There was a similar number of discontinuations at week 156 in both groups (Figure 2)
 - At 156 weeks, 15 participants remained in the not pretreated group (8 discontinued between weeks 104 and 156) and 16 remained in the glucocorticoid pretreated group (4 discontinued between weeks 104 and 156)

Table 1. Participant Demographics and Baseline Characteristics

	Not pretreated group (n=36)	Glucocorticoid 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)
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-A pain score, mean (SD)	6.4 (1.0)	6.8 (1.0)
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 knee OA, n (%)		
Unilateral	8 (22.2)	10 (27.8)
Bilateral	28 (77.8)	26 (72.2)
Follow-up, median (range), wk	142.5 (15, 156)	127 (8, 156)

BMI, body mass index; IQR, interquartile range; K-L, Kellgren-Lawrence; OA, osteoarthritis; SD, standard deviation; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Figure 2. Participant flow diagram.



*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. SAD, single ascending dose; TEAE, treatment-emergent adverse event.

METHODS

- Participants aged 30-80 years (N=72) with painful OA of the index knee and Kellgren-Lawrence grade 2 (mild), 3 (moderate), or 4 (severe) were enrolled into 2 groups (Figure 1)
 - Group 1: ultrasound-guided IA injection of PCRX-201 at low (1.4×10^{10} viral GC), middle (1.4×10^{11} viral GC), or high (1.4×10^{12} viral GC) dose
 - Group 2: same regimen and dosing, but preceded by IA glucocorticoid (methylprednisolone 40 mg) to test whether immune modulation improved vector tolerability and transduction
- Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain (WOMAC-A) and stiffness (WOMAC-B) subscale scores and Knee Injury and Osteoarthritis Outcome Score (KOOS) activities of daily living (ADL) were measured for up to 156 weeks
- Anti-Ad5 neutralizing antibody serum titers were measured at baseline and for up to 52 weeks

SAFETY

- **TEAEs:** the most commonly reported treatment-emergent adverse event (TEAE), index knee effusion, occurred less frequently in participants in the glucocorticoid pretreated (15/36; 42%) than the not pretreated (24/36; 67%) group (Table 2)
- **Treatment-related TEAEs:** index knee effusion events were considered treatment-related TEAEs in 13 of 36 participants (36%) in the glucocorticoid pretreated group and 22 of 36 participants (61%) in the not pretreated group
 - Among participants in the not pretreated group who had index knee effusion treatment-related TEAEs, 23% (5/22) were grade 1 (mild), 68% (15/22) were grade 2 (moderate), and 18% (4/22) were grade 3 (severe)
 - Among participants in the glucocorticoid pretreated group who had index knee effusion treatment-related TEAEs, 8% (1/13) were grade 1 (mild), 85% (11/13) were grade 2 (moderate), and 8% (1/13) were grade 3 (severe)
 - Treatment-related index knee effusion TEAEs resolved in a median of 21 days in the not pretreated group (range, 2-165 days) and in a median of 22.5 days for the glucocorticoid pretreated group (range, 3-111 days)

Table 2. Summary of TEAEs, SAEs, TEAEs Grade ≥3, and TEAEs Occurring in ≥10% of Participants in Any Pretreatment Group

	Not Pretreated			Glucocorticoid pretreated		
	Low (n=12)	Middle (n=16)	High (n=8)	Low (n=13)	Middle (n=15)	High (n=8)
≥1 TEAE	11 (91.7)	16 (100)	8 (100)	12 (92.3)	14 (93.3)	8 (100)
≥1 SAE	3 (25)	1 (6.2)	1 (12.5)	1 (7.7)	2 (13.3)	2 (25)
≥1 TEAE grade ≥3	3 (25)	3 (18.8)	3 (37.5)	2 (15.4)	4 (26.7)	2 (25)
≥1 TEAE occurring in ≥10% of participants in either pretreatment group						
Joint effusion	6 (50)	10 (62.5)	8 (100)	5 (38.5)	5 (33.3)	5 (62.5)
Arthralgia	6 (50)	4 (25)	1 (12.5)	5 (38.5)	5 (33.3)	6 (75)
Joint swelling	7 (58.3)	1 (6.2)	1 (12.5)	0 (0)	2 (13.3)	0 (0)
Headache	2 (16.7)	1 (6.2)	2 (25)	1 (7.7)	2 (13.3)	1 (12.5)
Back pain	0 (0)	0 (0)	2 (25)	2 (15.4)	1 (6.7)	1 (12.5)
Fall	1 (8.3)	0 (0)	1 (12.5)	2 (15.4)	2 (13.3)	0 (0)
Osteoarthritis	0 (0)	0 (0)	0 (0)	1 (7.7)	2 (13.3)	3 (37.5)
Hypertension	2 (16.7)	2 (12.5)	0 (0)	1 (7.7)	0 (0)	0 (0)
Synovial cyst	3 (25)	1 (6.2)	1 (12.5)	0 (0)	0 (0)	0 (0)
Musculoskeletal pain	0 (0)	0 (0)	0 (0)	2 (15.4)	0 (0)	2 (25)

SAE, serious adverse event; TEAE, treatment-emergent AE. Data are the n (%), where n is the number of participants in each category. Participants who reported ≥1 TEAE are counted only once per category. n in the column headings is the number of participants in each steroid-pretreatment status and dose cohort and is the denominator for percentages.

EFFICACY

- Improvements in pain and function were observed at all doses and across both the not pretreated and glucocorticoid pretreated groups up to 156 weeks after PCRX-201 IA injection (Figures 3-6)

WOMAC-A pain and WOMAC-B stiffness

- The glucocorticoid pretreated group demonstrated greater improvements for WOMAC-A pain versus the not pretreated group (range of least squares mean [LSM] reduction from baseline pain as observed across dose levels, 3.37-3.62 [of 10] points vs 2.30-2.55 points; Figure 3)
- LSM improvements across the 3 doses were observed for WOMAC-B stiffness scores at 156 weeks in both the not pretreated group (2.23-3.06-point reduction from baseline stiffness as observed) and the glucocorticoid pretreated group (3.31-4.13-point reduction from baseline stiffness as observed; Figure 3)
- Participants in the pretreated group with K-L grade of 2, 3, and 4 showed LSM reductions from baseline in WOMAC-A pain and WOMAC-B stiffness (Figure 4), with greater numerical reductions observed in those with K-L grade 2 than those with K-L grades 3 or 4

Figure 1. Study design.

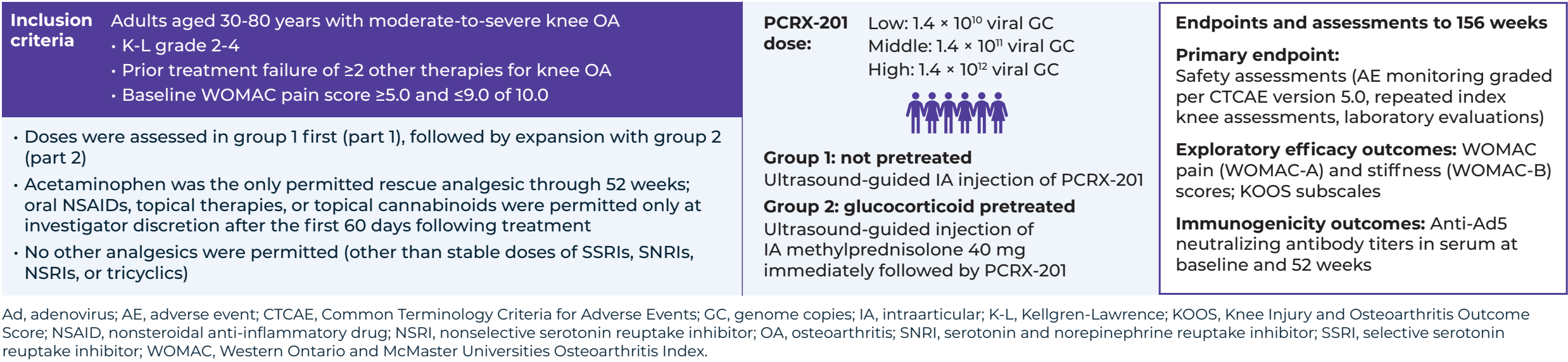
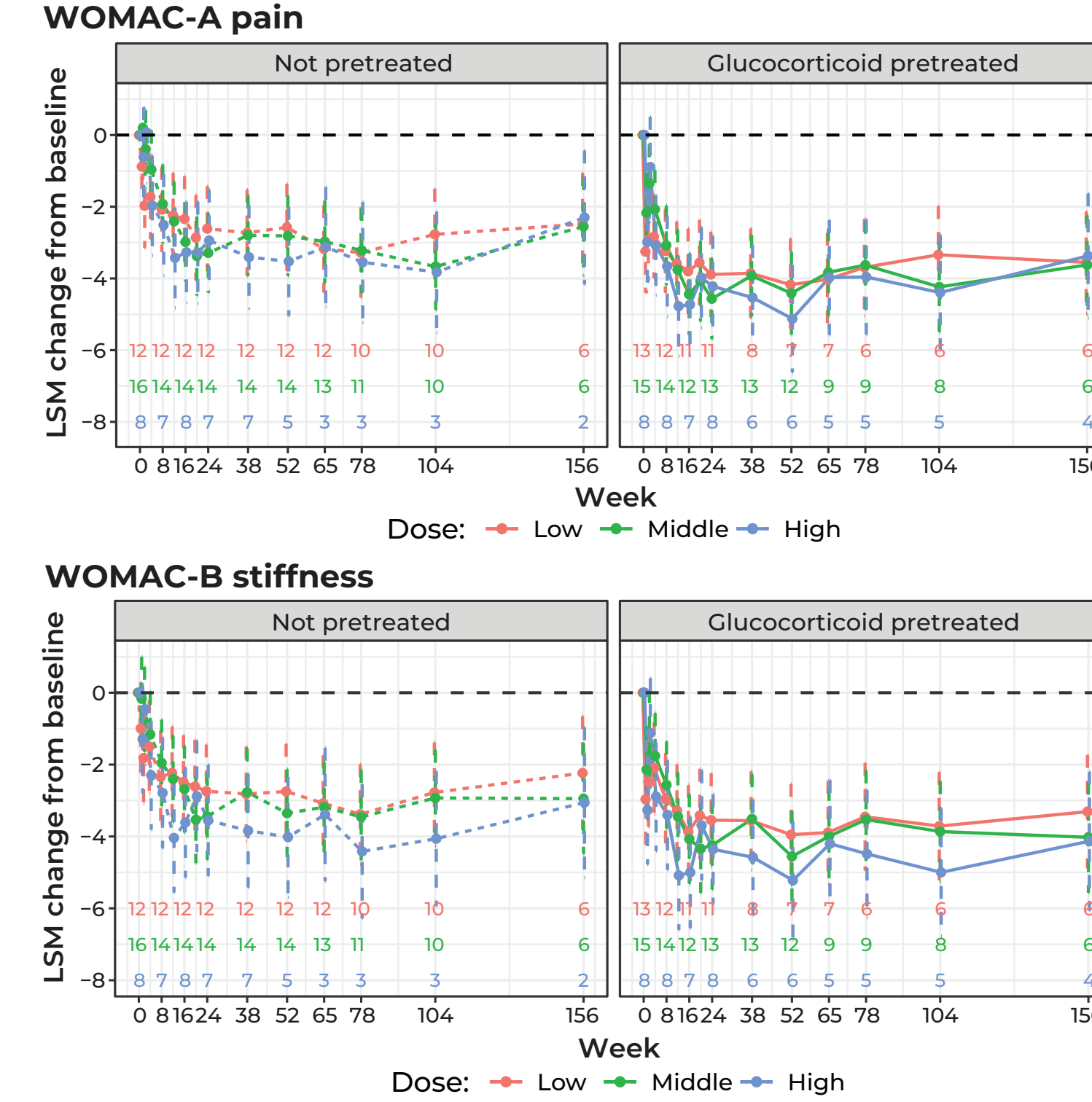
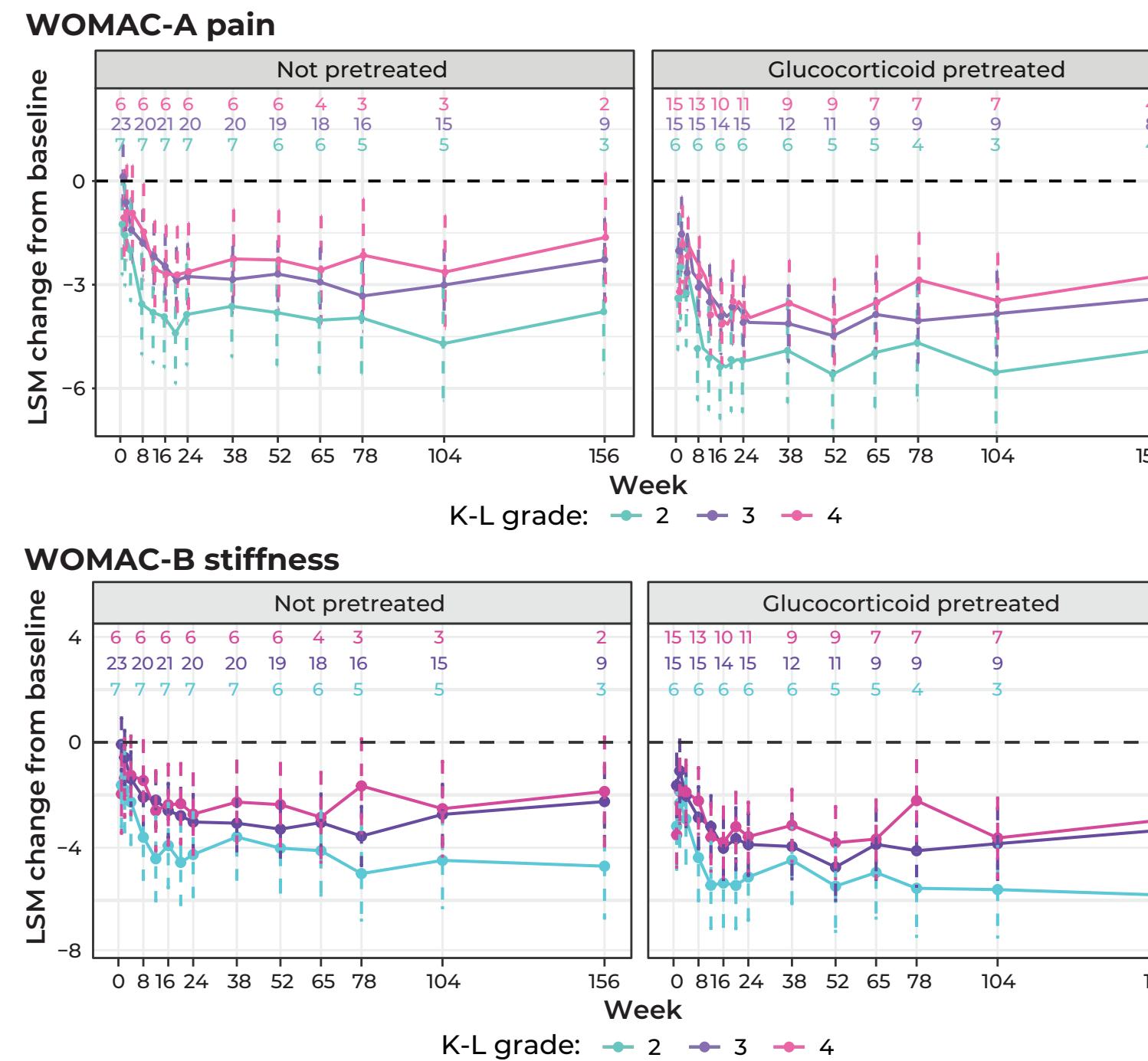


Figure 3. LSM change from baseline for WOMAC-A pain scores and WOMAC-B stiffness scores by dose.



The number of participants with WOMAC results may be different than enrollment totals because of participants still enrolled who did not attend the week-156 visit or participants who discontinued after attending the week-156 visit. Values in color are the sample size over time. Error bars are the 95% confidence interval. LSM, least squares mean; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Figure 4. WOMAC-A pain and WOMAC-B stiffness by K-L grade.

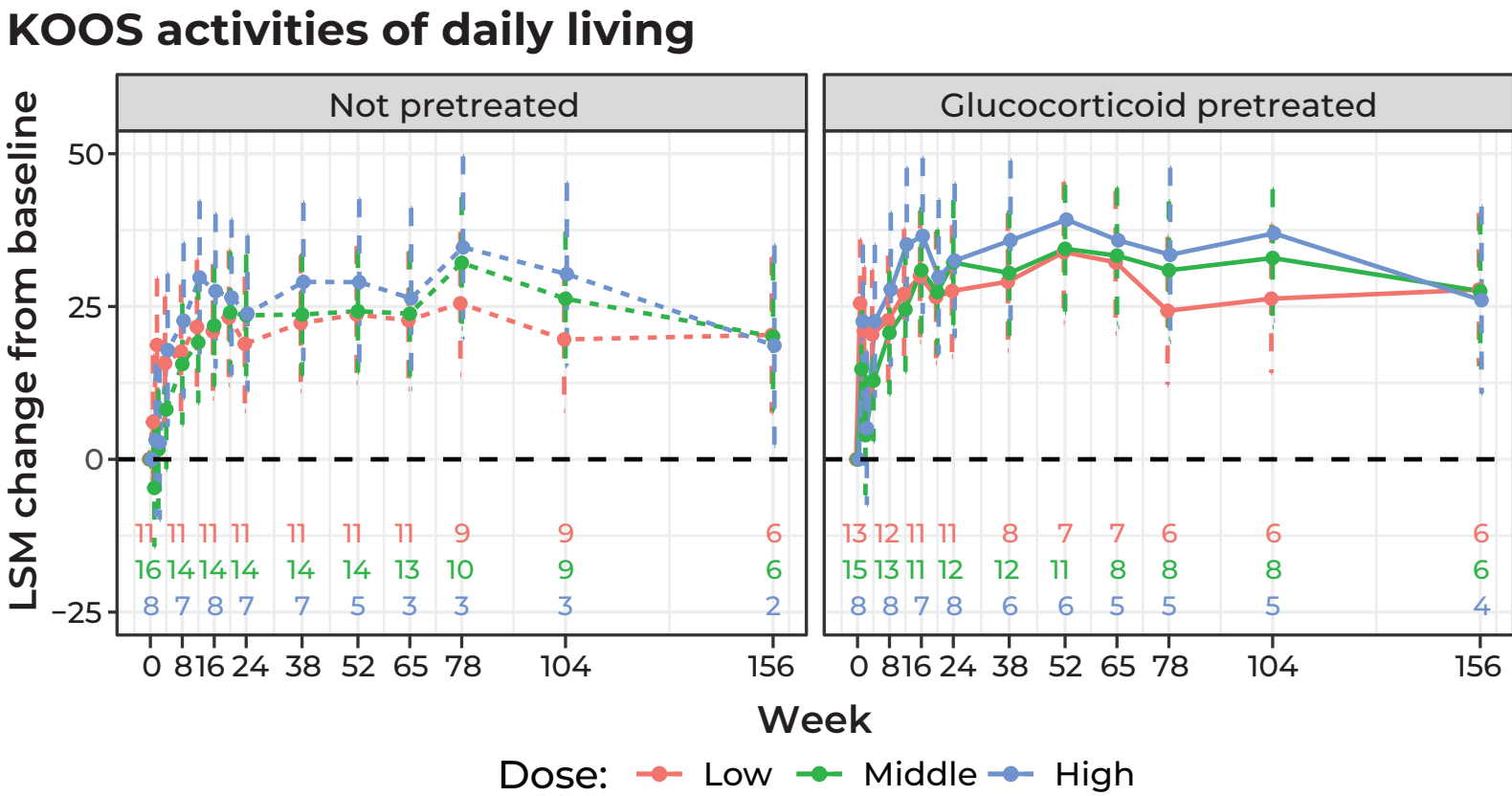


Values in color are the sample size over time. Error bars are the 95% confidence interval. K-L, Kellgren-Lawrence; LSM, least squares mean; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

FUNCTION

- **KOOS:** at 156 weeks, LSM improvements across the 3 doses were observed for KOOS ADL scores in both the not pretreated (range, 18.82-20.24 [of 100] points) and the glucocorticoid pretreated group (range, 26.07-27.48 points; Figure 5)

Figure 5. LSM change from baseline for KOOS ADL.

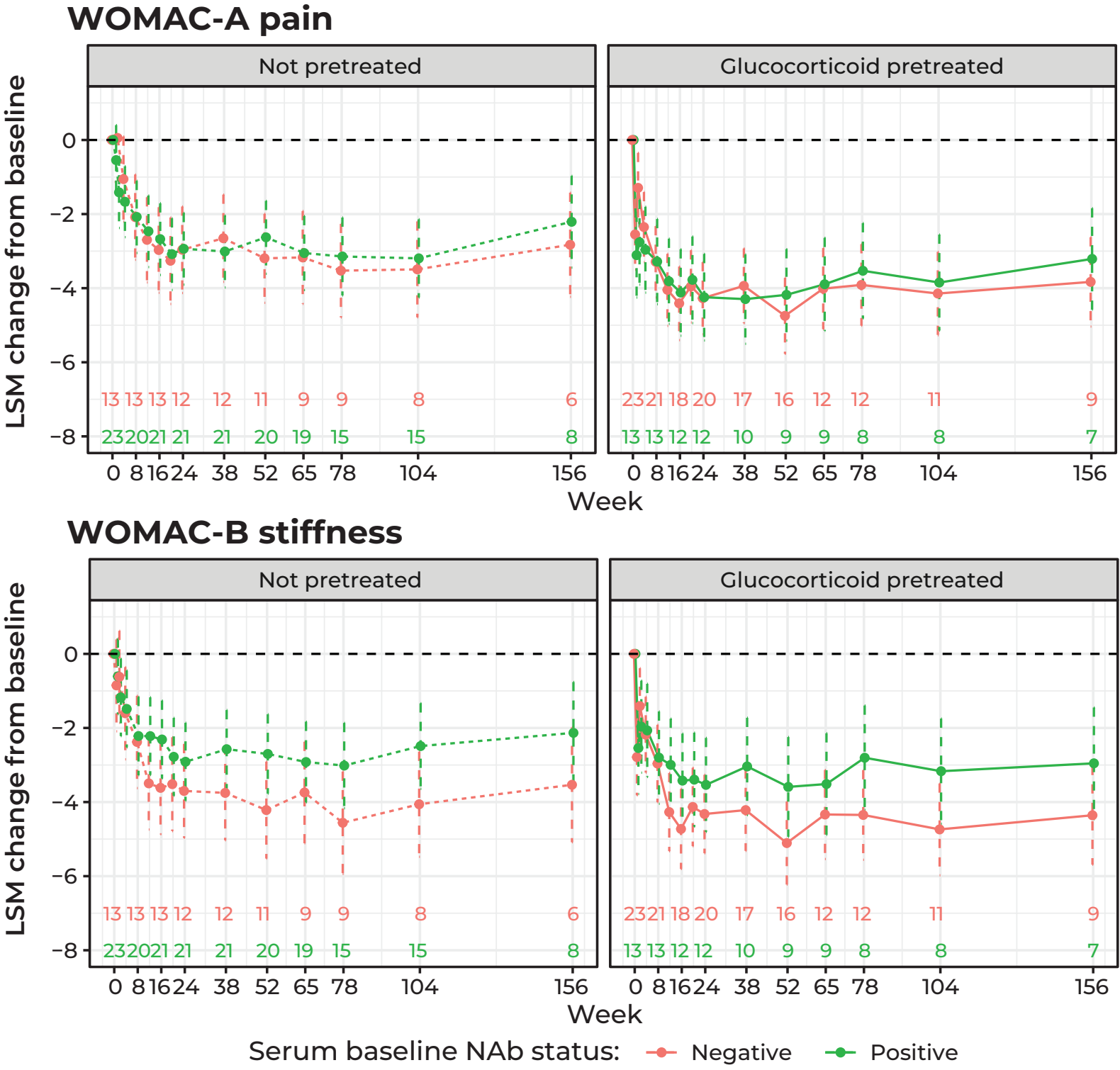


The number of individuals with KOOS results may be different than enrollment totals because of participants still enrolled who did not attend the week-156 visit or participants who discontinued after attending the week-156 visit. Values in color are the sample size over time. Error bars are the 95% confidence interval. ADL, activities of daily living; LSM, least squares mean; KOOS, Knee Injury and Osteoarthritis Outcome Score.

IMMUNOGENICITY

- Importantly, preexisting serum neutralizing antibodies did not affect PCRX-201 efficacy as determined by WOMAC-A pain and WOMAC-B stiffness (Figure 6)

Figure 6. LSM change from baseline for WOMAC-A pain scores and WOMAC-B stiffness scores by serum baseline NAb status.



Values in color are the sample size over time. Error bars are the 95% confidence interval. LSM, least squares mean; NAb, neutralizing antibody; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.