Disclosure Information

Stanley Cohen, MD
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I have a financial relationship(s) with:

Investigator, Pacira BioSciences, Inc.

AND

My presentation does include a discussion of investigational use.

PCRX201 is utilized in a phase 1, open-label, single ascending dose study

SAFETY AND PRELIMINARY EFFICACY OF PCRX201, AN INTRA-ARTICULAR GENE THERAPY FOR KNEE OSTEOARTHRITIS: A PHASE 1, OPEN-LABEL, SINGLE ASCENDING DOSE STUDY

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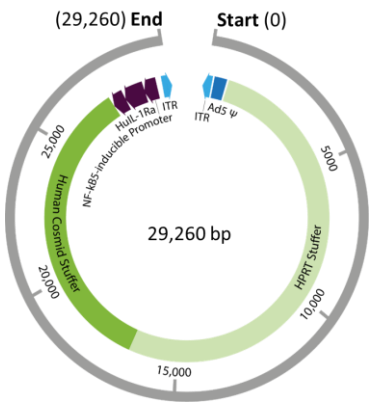
Background

IL-1 may be an important driver of inflammation, pain, and potentially disease progression in OA.[1] Gene therapy has the potential to offer long-term expression of a therapy at the disease site.[2]



PCRX201

- Novel helper-dependent adenovirus therapy[1]
- Devoid of viral elements except for the following[1]:
  - Nonintegrateable double-stranded DNA coding for the human IL-1Ra gene
  - Inducible NF-κB promoter turns on gene expression during inflammation (reflects natural response)
- In vivo transduction enables local IL-1Ra gene expression in the presence of inflammation[2]
- IL-1Ra competitively blocks binding of both IL-1α and IL-1β, while having no inherent signaling capabilities itself[1]

A preliminary study in an ACLT rat OA model found that a rat surrogate of PCRX201 mitigated OA-related joint damage and remained localized to the joint space, with a tolerable safety profile[1]

Here, we report preliminary safety and efficacy results from a phase 1, open-label, single ascending dose study of PCRX201 in knee OA (NCT04119687)

ACLT, anterior cruciate ligament transection; IL-1Ra, interleukin 1 receptor antagonist; IL-1RI, interleukin 1 receptor type I; NF-κB, nuclear factor κ-light chain enhancer of activated B cells; OA, osteoarthritis.

1. Senter et al. *Hum Gene Ther*. 2022;33(9-10):541-549; **2.** Mehta et al. *Curr Opin Rheumatol*. 2021;33(1):94-109.

Open-label Study Design

Inclusion criteria

- Adults aged 30 to 80 years with moderate-to-severe knee OA
- K/L scale grade 2-4
- Prior treatment failure of ≥2 other therapies for OA
- Baseline WOMAC pain score ≥4.0 and ≤9.0

Outcomes

- Primary endpoint: safety assessments including AE monitoring, repeated index knee assessments, laboratory evaluations, and biodistribution samples
- Efficacy was assessed primarily as change from baseline in WOMAC pain score*
- Quantitative MRIs were obtained at baseline and week 52

Study design

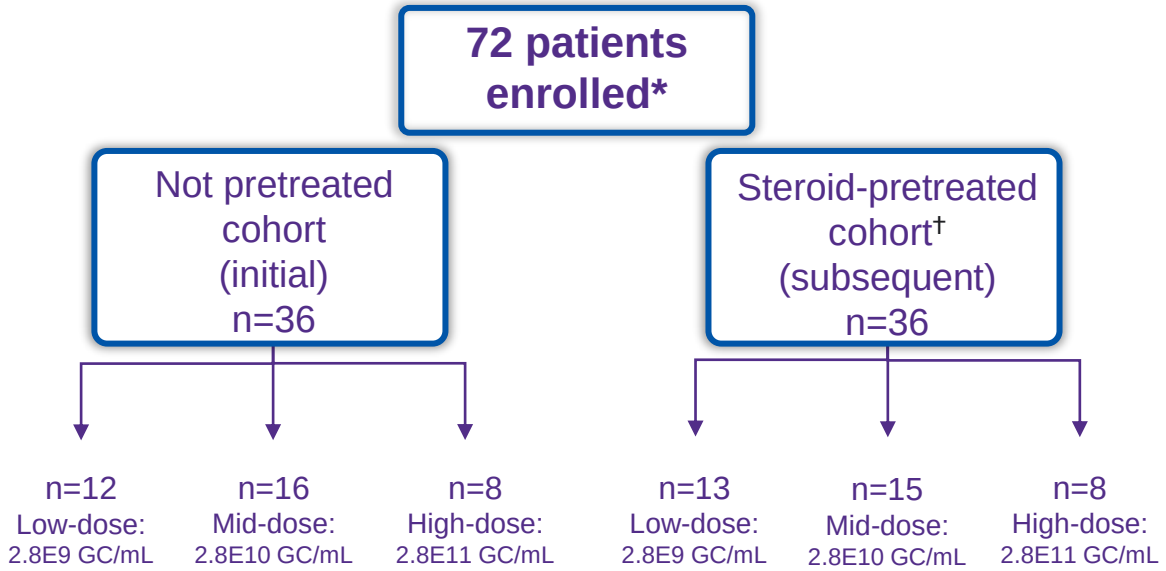
Cohort 1: Not pretreated (n=36)
PCRX201 IA ultrasound-guided injection

Cohort 2: Steroid-pretreated (n=36)
IA methylprednisolone 40 mg immediately before PCRX201 administration

- Three different doses of PCRX201 were used (low, mid, high)
- Allocation was nonrandomized (doses assessed in not pretreated cohort first, followed by expansion with a steroid-pretreated cohort)
- Acetaminophen was the only permitted rescue analgesic
- No other analgesics were permitted (other than stable doses of SSRIs, SNRIs, NSRIs, or tricyclics) for the first 52 weeks†

*WOMAC assessed at weeks 1, 2, 4, 8, 12, 16, 20, 24, 38, 52, 65, 78, and 104. †NSAIDS were allowed at the discretion of the investigator after day 60. AE, adverse event; IA, intra-articular; K/L, Kellgren/Lawrence; 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.

Patient Disposition and Baseline Characteristics



	Not pretreated cohort (n=36)	Steroid-pretreated cohort (n=36)
Median (range) follow-up, wk	64.9 (15.1-106.1)	37.6 (7.6-52.0)
Discontinuations, n (%)	13 (36)	11 (31)
Participant withdrew consent, n	9	7
Lost to follow-up, n	3	1
Adverse event (unrelated to treatment), n	1	1
Withdrawn by investigator or sponsor, n	0	1
Death (unrelated to treatment), n	0	1

	Not pretreated cohort (n=36)	Steroid-pretreated cohort (n=36)
Median age (IQR), y	62.0 (58.5-67.0)	67.5 (58.5-71.5)
Gender, 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)

*The first patient was dosed in March 2020, and the last patient was dosed in December 2021. Data cutoff is July 2022. †Intra-articular injection of 40 mg of methylprednisolone immediately before PCRX201 administration. BMI, body mass index; IQR, interquartile range; K/L, Kellgren/Lawrence; SD, standard deviation; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Summary of Treatment-Related Adverse Events (TRAEs)

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)
Mid-dose	9/16 (56)	4/15 (27)
High-dose	8/8 (100)	5/8 (63)
Severity of knee effusion, n/N (%)*		
Grade 1	6/23 (26)	1/13 (8)
Grade 2	12/23 (52)	11/13 (92)
Grade 3	5/23 (22)	1/13 (8)

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 (3)	1/36 (3)
Flu-like symptoms, n/N (%)		
High-dose	-	1/36 (3)
Self-limited fever, n/N (%)†		
Mid-dose		1/36 (3)
Severe injection pain, n/N (%)‡		
Mid-dose	-	1/36 (3)

Decreased incidence and severity of index knee events were observed in the steroid-pretreated cohort compared with the not pretreated cohort

93.2% of knee-related TRAEs resolved with rest, ice, acetaminophen, or aspiration of synovial fluid; all Grade 3 knee-related AEs resolved with intra-articular steroids

*Severity determined by principal investigator using medical judgment and general guidelines from CTCAE v5.0. †Fever at onset of knee AE. ‡Resulted in early termination of injection with no related knee AEs.

Preliminary Data to Assess the Impact of Baseline Systemic NAbs on Safety and WOMAC Scores

- Preliminary immunogenicity data include the first 13 patients (5 low dose and 8 moderate dose), assessed at week 26

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

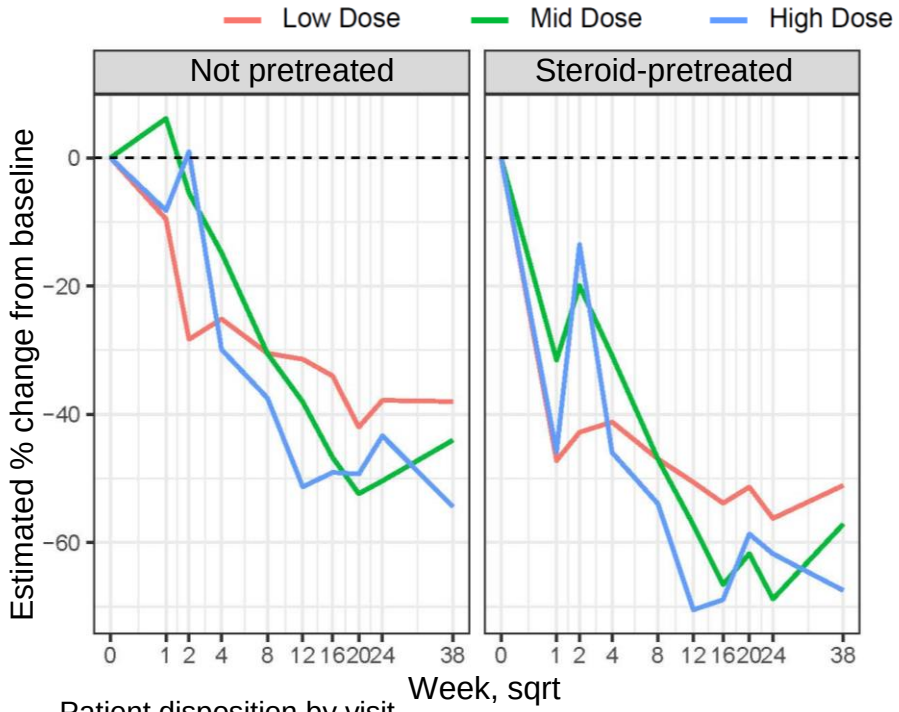
Systemic NAb positivity at baseline versus responder status

Systemic NAb	Any substantial responder*	No substantial responder*
Positive, n	3	4
Negative, n	4	2

From this initial sample set, systemic baseline NAb positivity does not appear to have a notable impact on risk of knee-related AEs or WOMAC response

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

% Change in WOMAC-A From Baseline by Dose and Treatment*



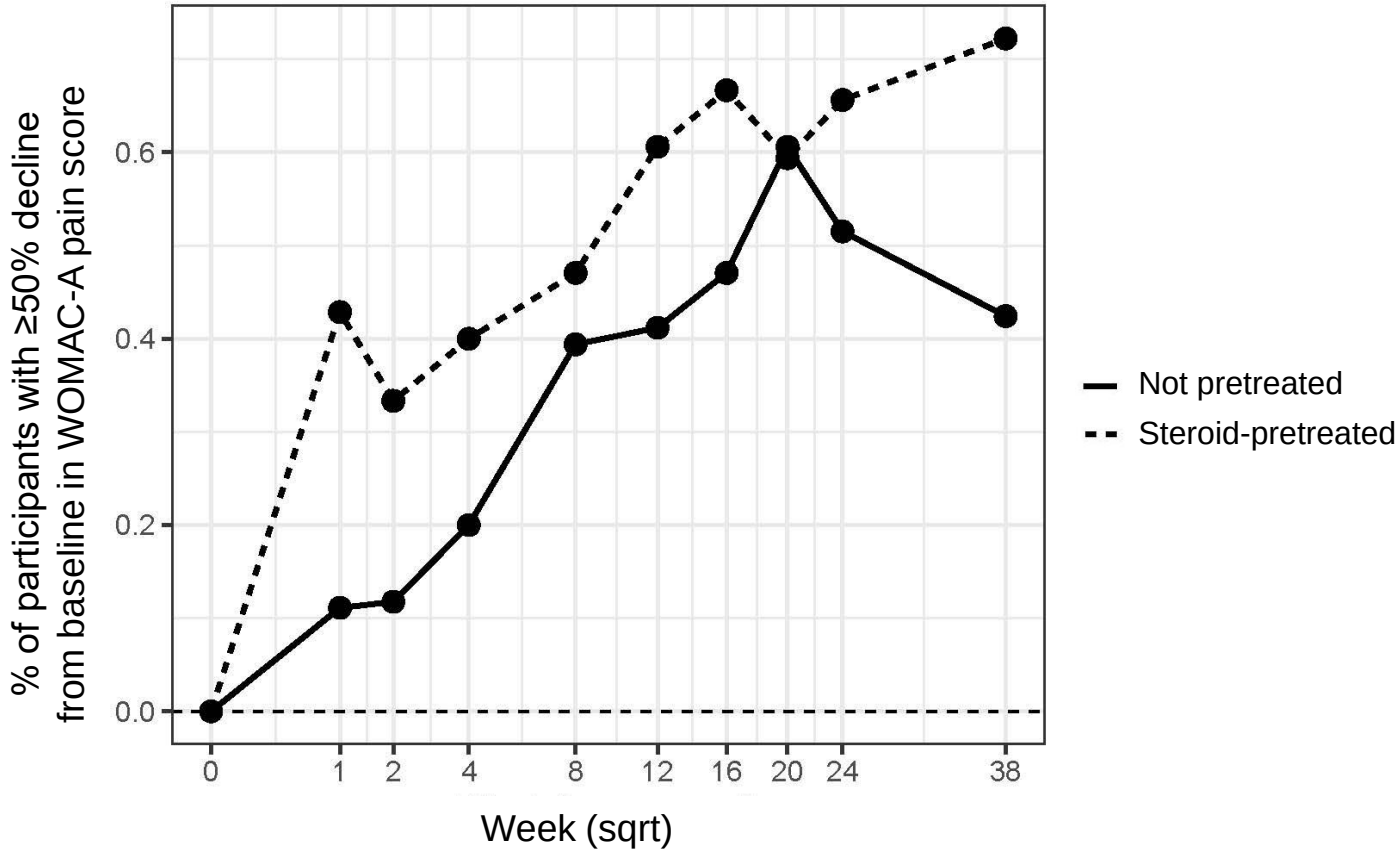
Patient disposition by visit

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	Mid 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	Mid 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

Improvements in knee pain were observed across all dose groups and cohorts receiving PCRX201
Pretreatment with steroids did not appear to impact transduction of PCRX201

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

WOMAC-A Pain Score: Percentage of Patients With ≥50% Decline From Baseline*



Preliminary efficacy results suggest substantial improvement in pain across all PCRX201 cohorts

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

Conclusions

1. PCRX201 was generally well tolerated, with main TRAEs including index knee pain and effusion, which generally resolved within weeks with conservative care or IA steroids
2. There were no treatment-related SAEs, deaths, or late recurrences and no unusual patterns of nonrelated AEs in follow-up
3. A decreased incidence of overall and grade 3 index knee events was observed in the steroid-pretreated cohort compared with the not pretreated cohort
4. 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

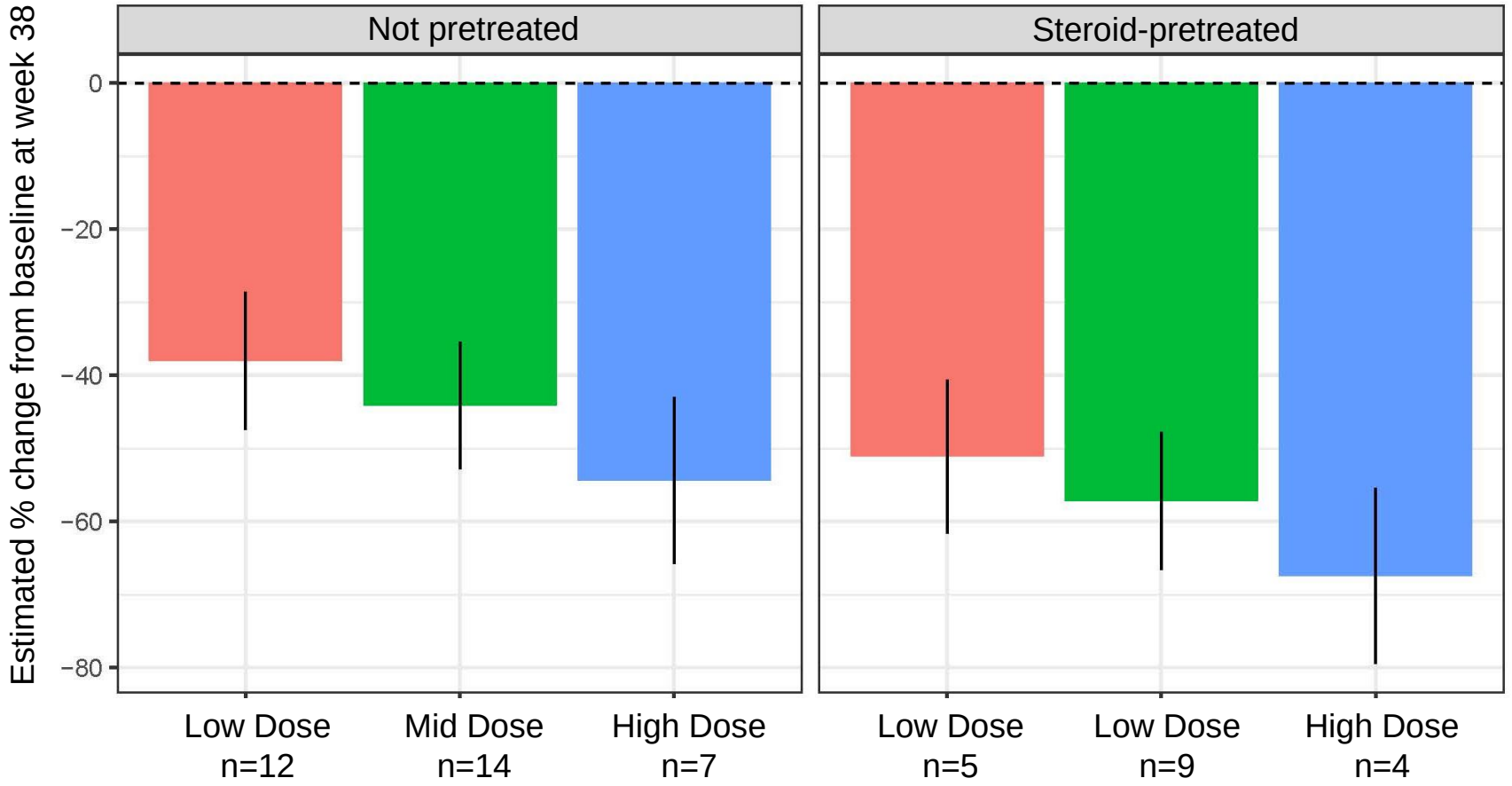
Preliminary results from this phase 1 open-label study of PCRX201 are promising and support further investigation of PCRX201 for knee OA
This study is ongoing, and patients will be followed for 5 years

AE, adverse event; IA, intra-articular; OA, osteoarthritis; SAE, severe adverse event; TRAE, treatment-related AE.

Thank you!

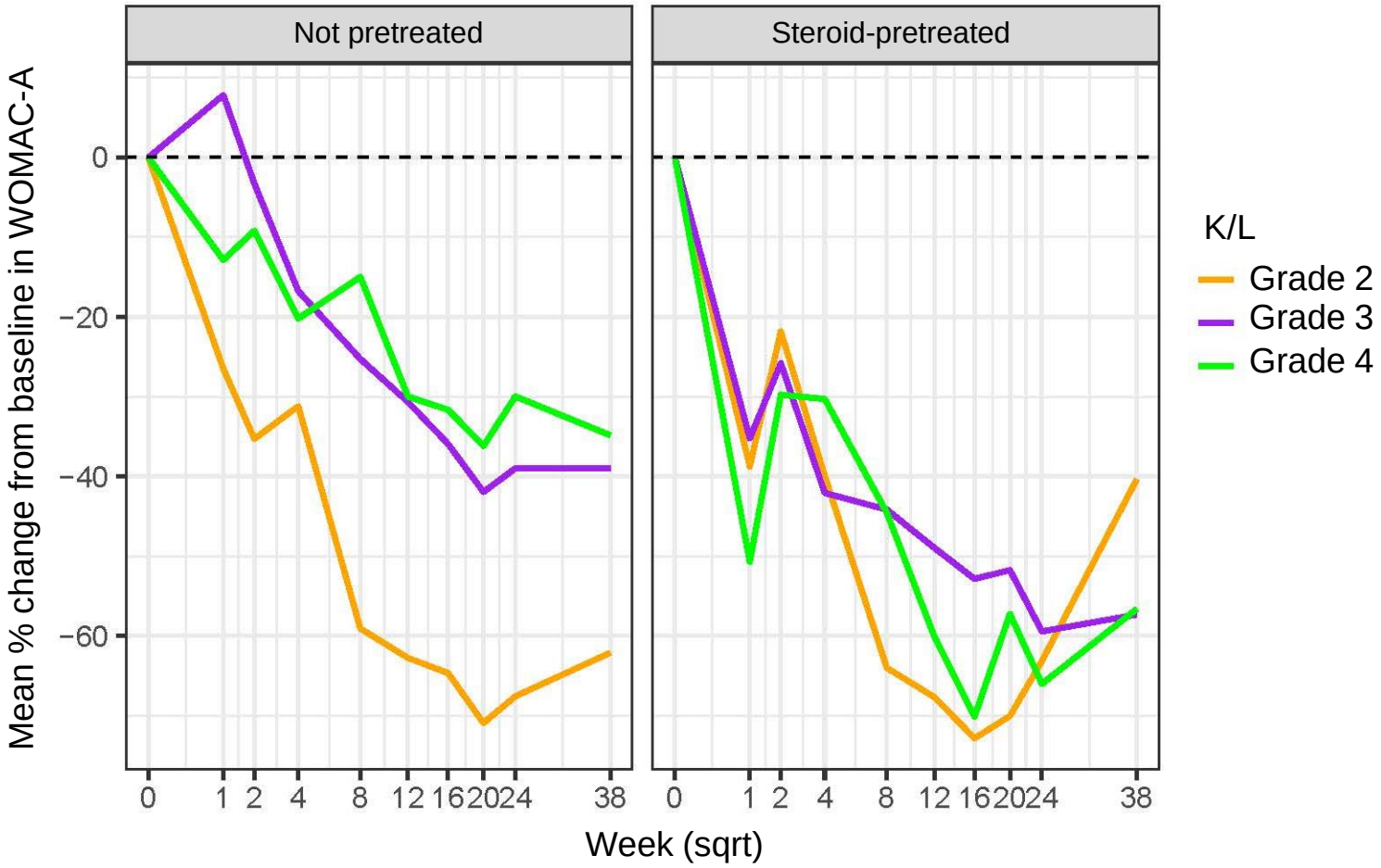
Backup

% Change in WOMAC-A at Week 38 by Dose and Treatment



WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Change in WOMAC-A Pain Scores by K/L Grade*



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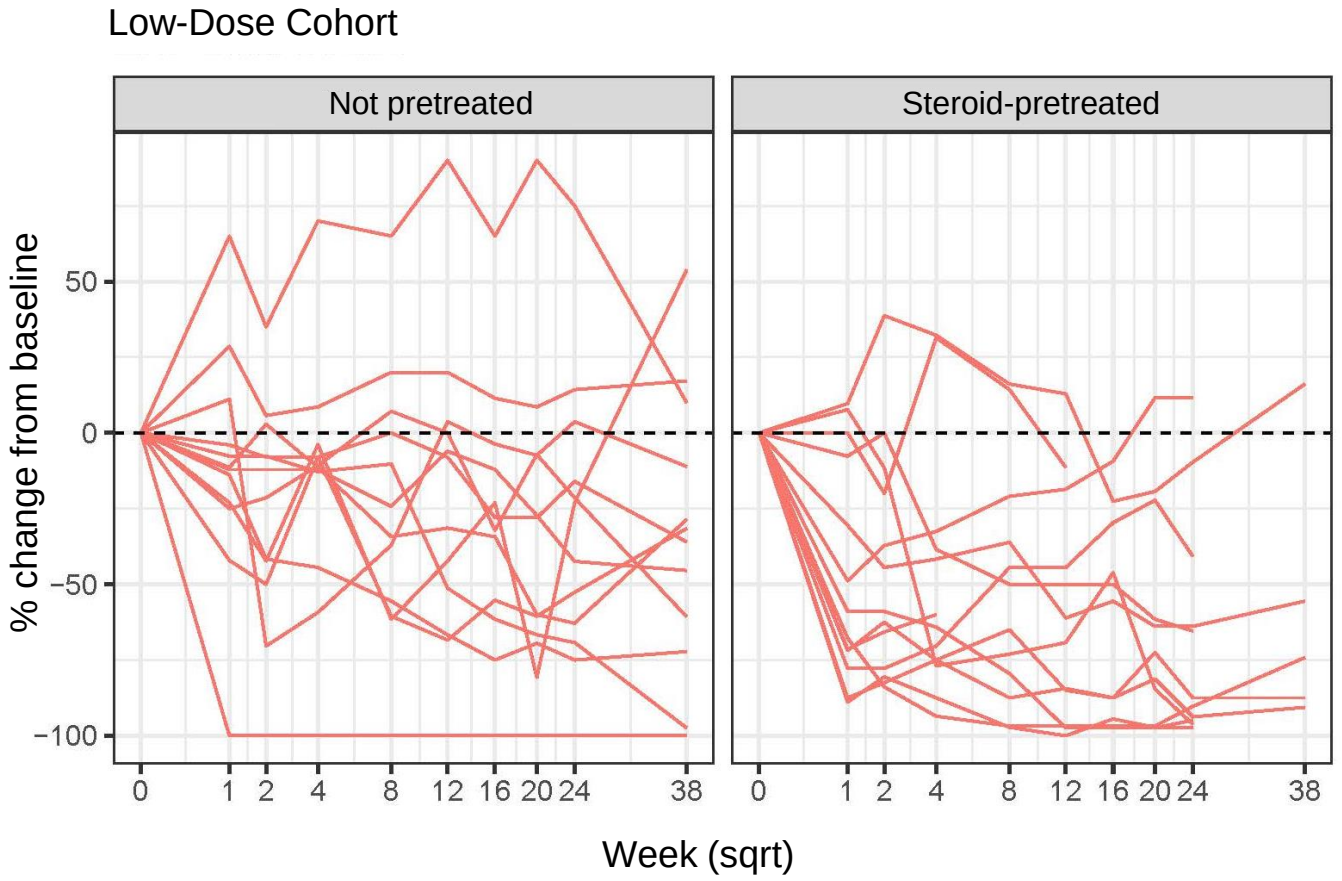
WOMAC-A Pain Score: Mean Percent Change From Baseline in the Not Pretreated and Steroid-Pretreated Low-Dose Cohorts*



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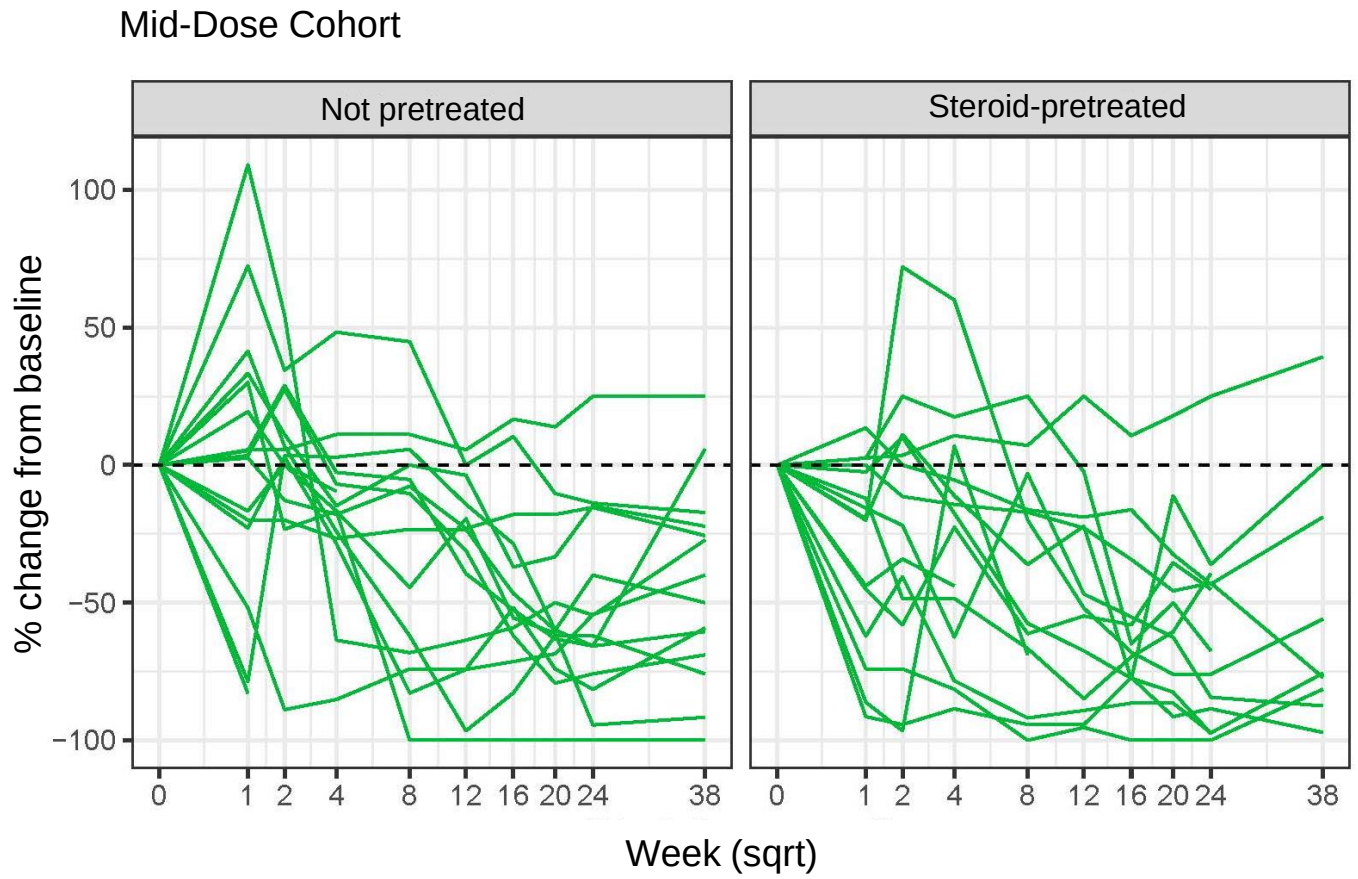

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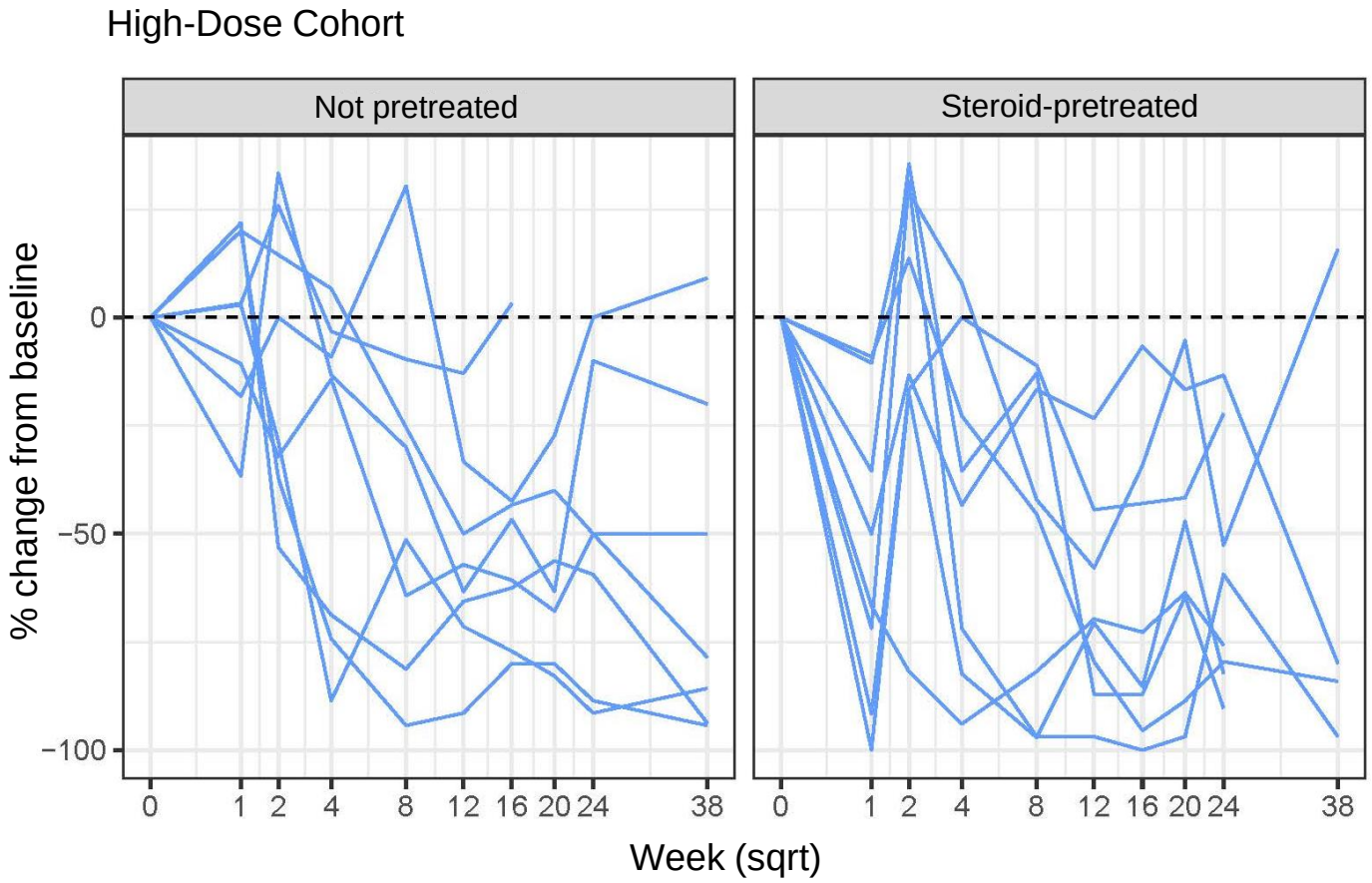

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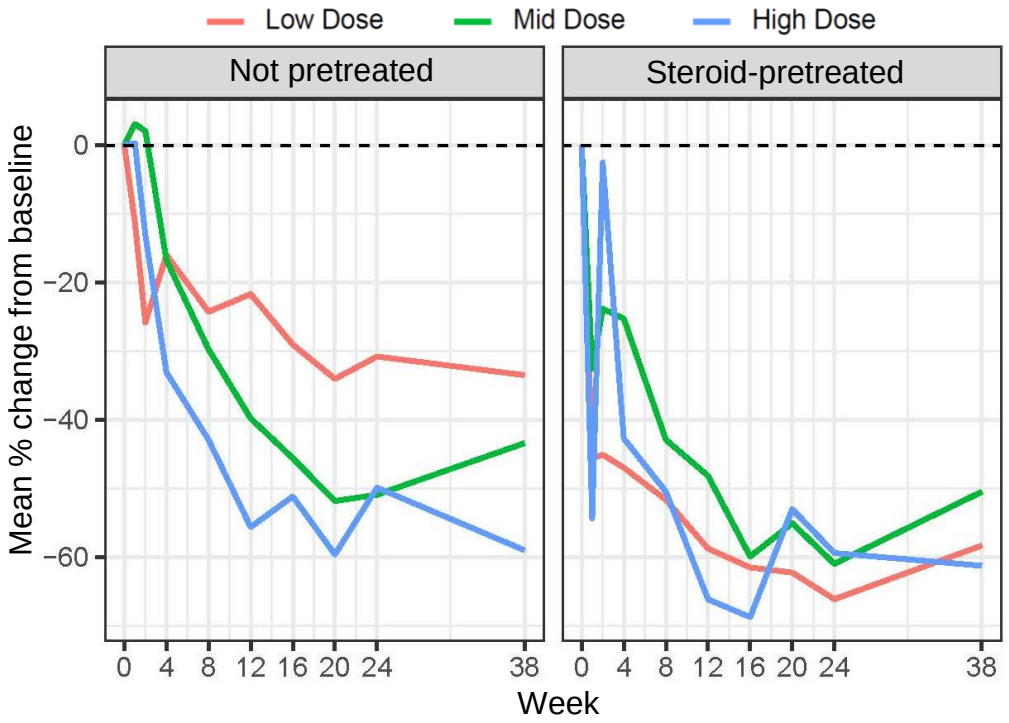
Change from WOMAC-A Baseline in the 2 Cohorts*



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Steroid−pretreated	Low Dose	13	13	13	12	12	12	11	11	11	5
Steroid−pretreated	Mid 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

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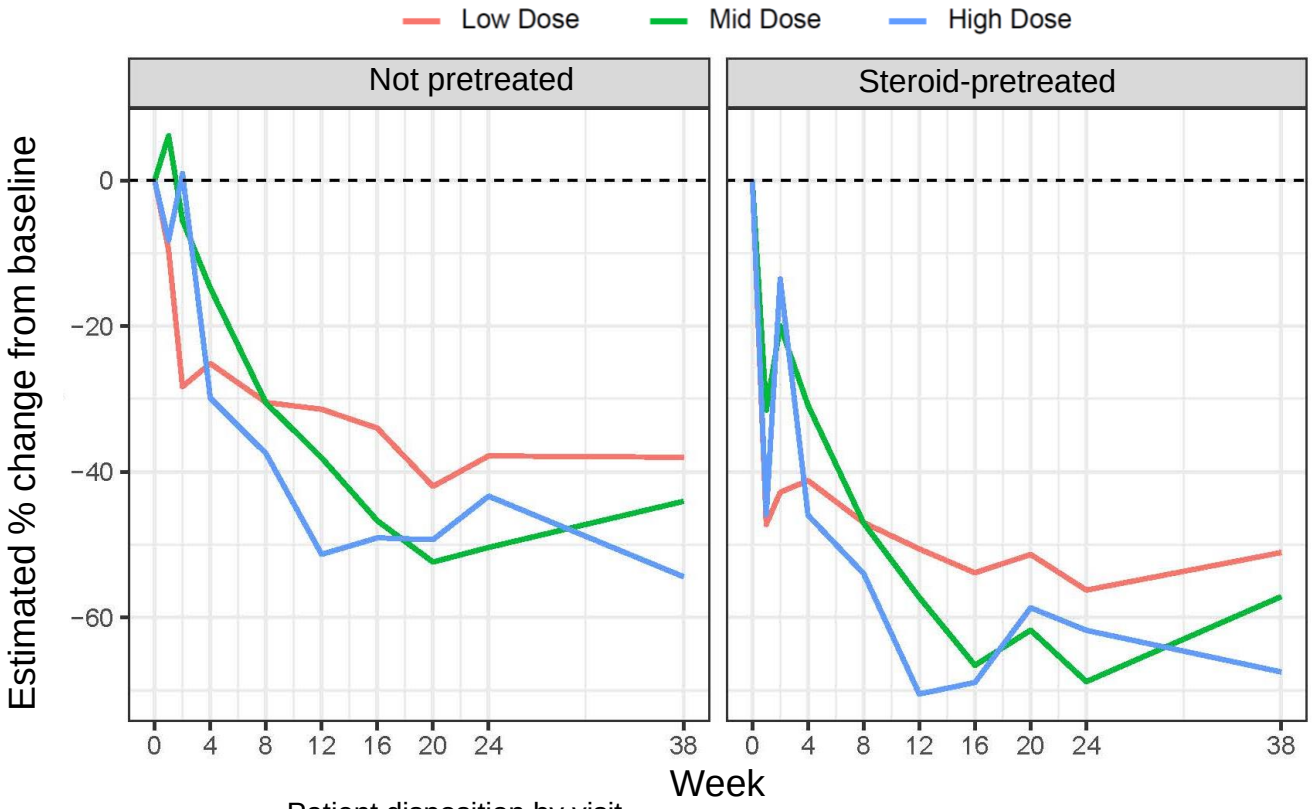
% Change in WOMAC-A by Dose and Treatment*



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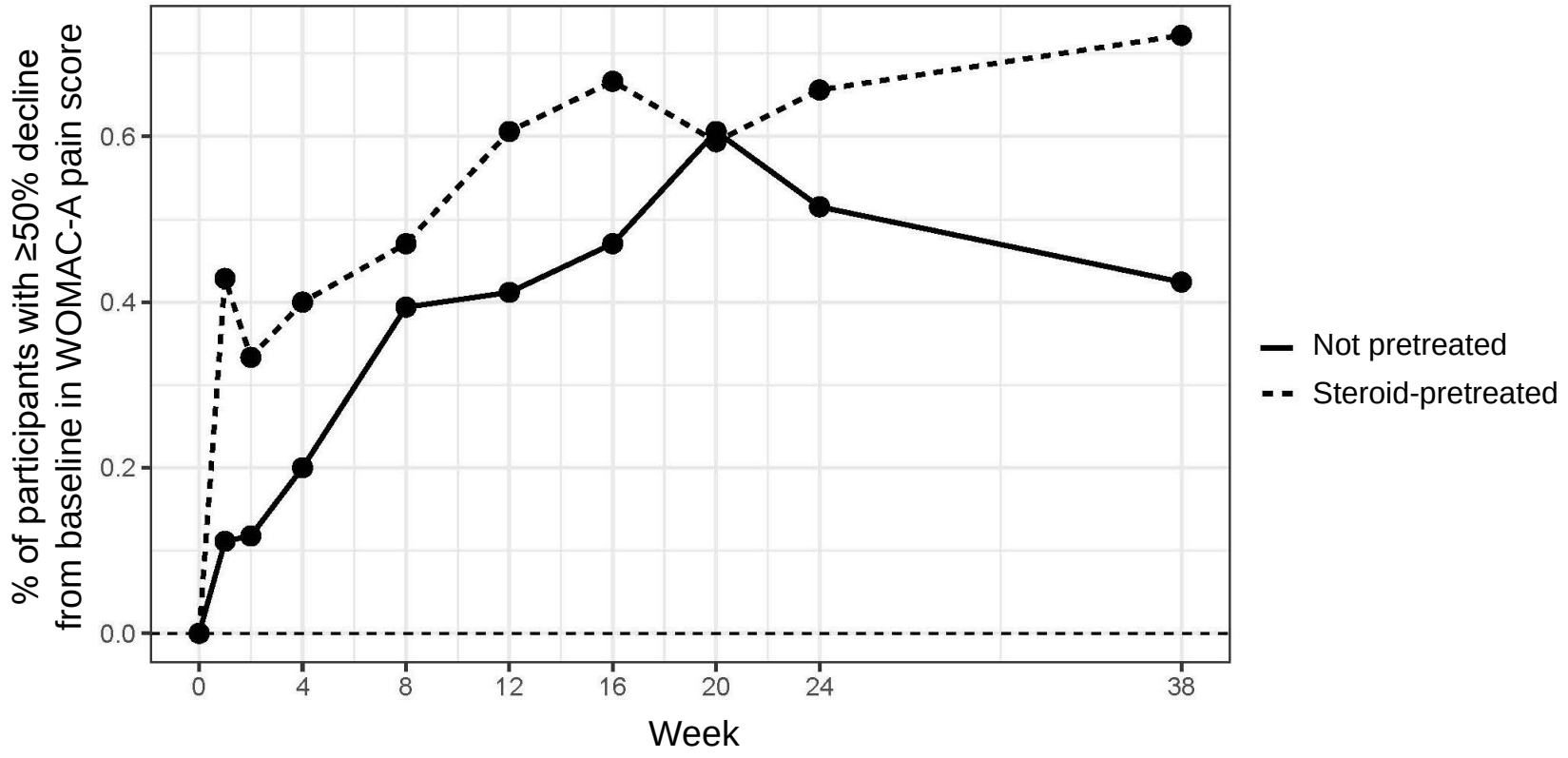

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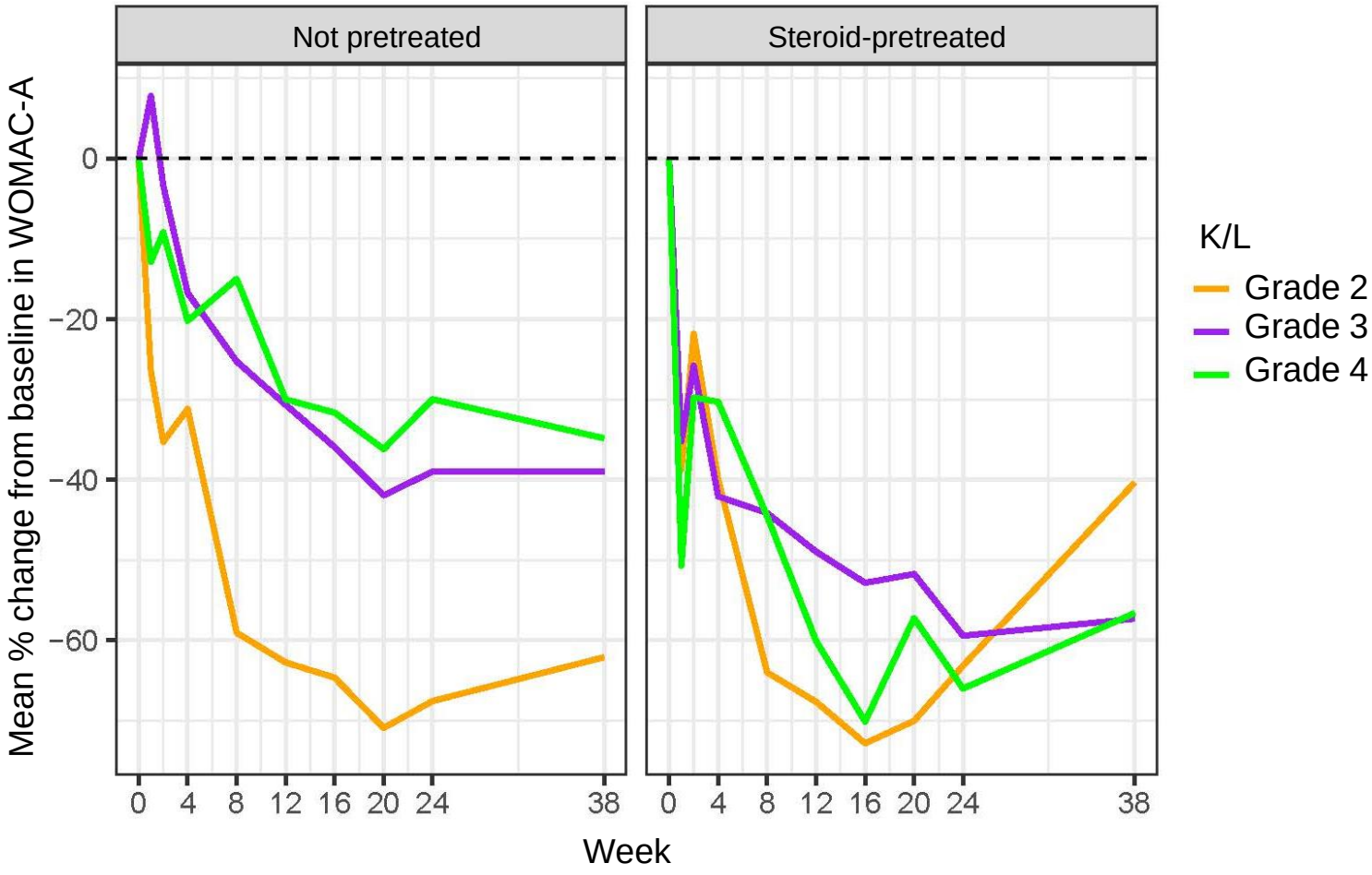

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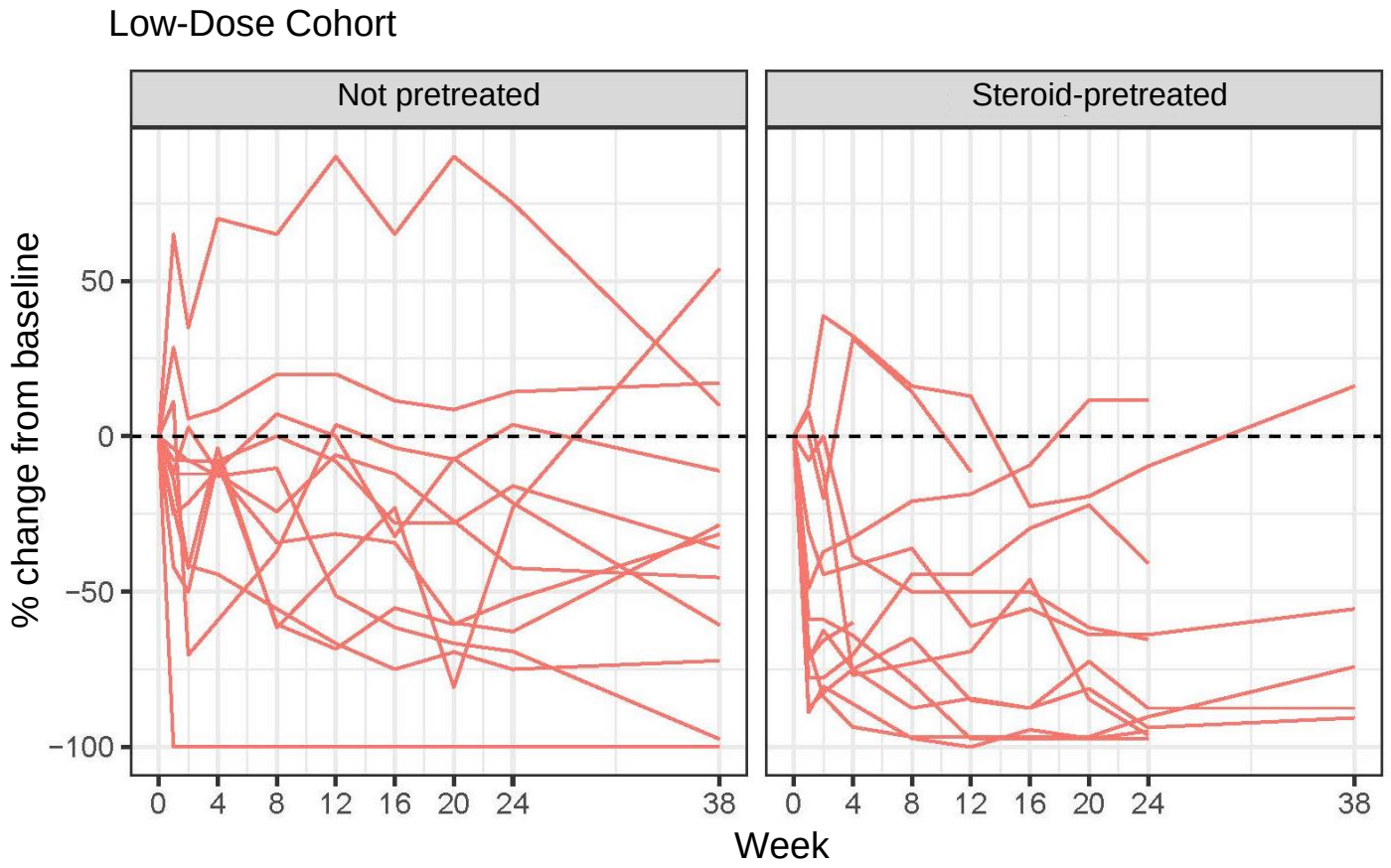

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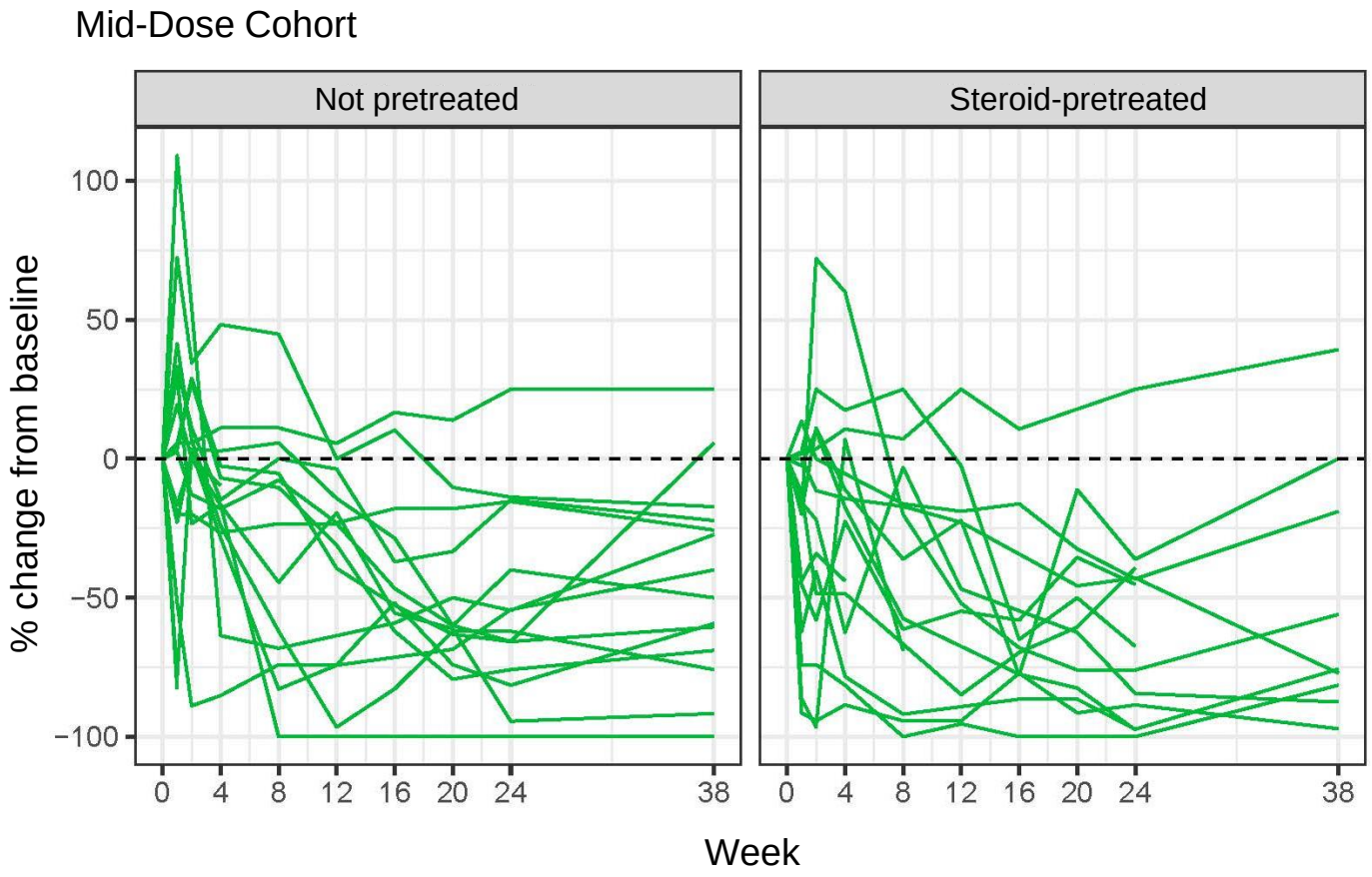

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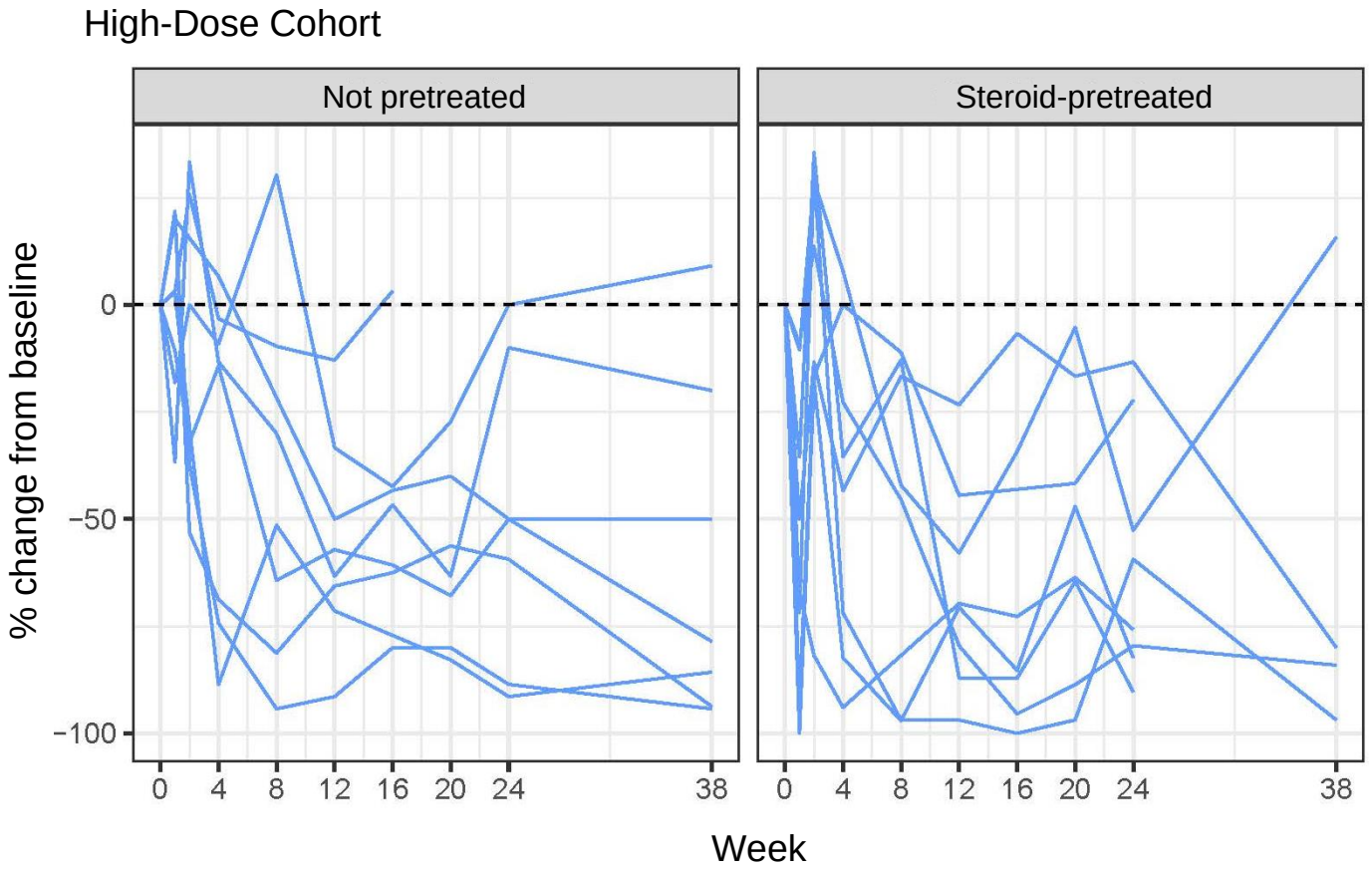

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