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New Therapies in Development for Osteoarthritis

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Title & Affiliation

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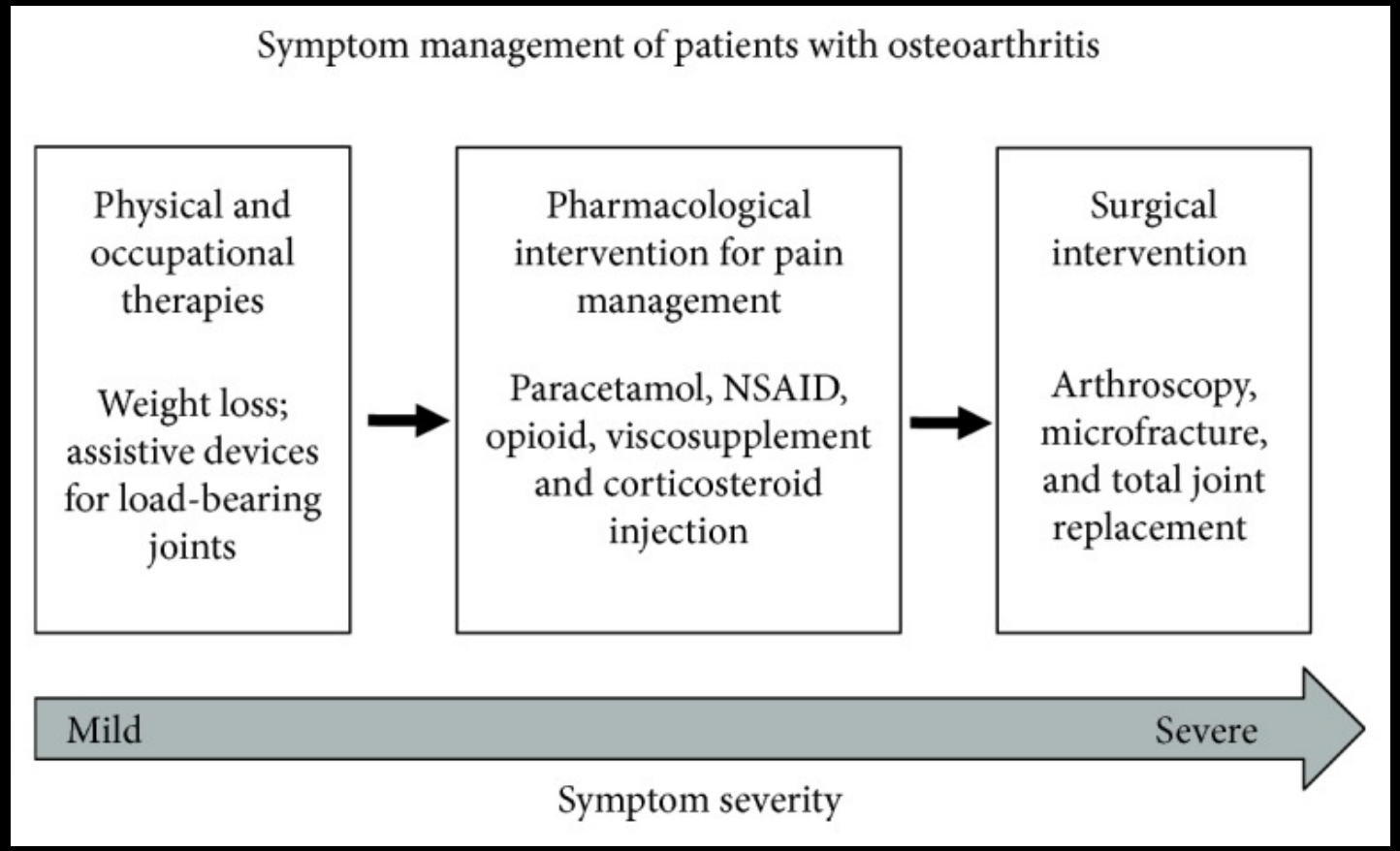
Disclosure

- Consultant/Independent Contractor: Samumed
- Scientific Advisory Board and Consultant: Unity
- Honoraria: Pfizer
- Speakers Bureau: Pfizer

Learning Objectives

- Summarize the results of studies of the new therapies in clinical development for osteoarthritis


Symptom management of patients with osteoarthritis
Physical and occupational therapies
Weight loss; assistive devices for load-bearing joints
Pharmacological intervention for pain management
Paracetamol, NSAID, opioid, viscosupplement and corticosteroid injection
Surgical intervention
Arthroscopy, microfracture, and total joint replacement
Mild
Severe
Symptom severity

Novel intra-articular and systemic therapies, and in Phase II and III studies, are they promising?

Wnt modulator

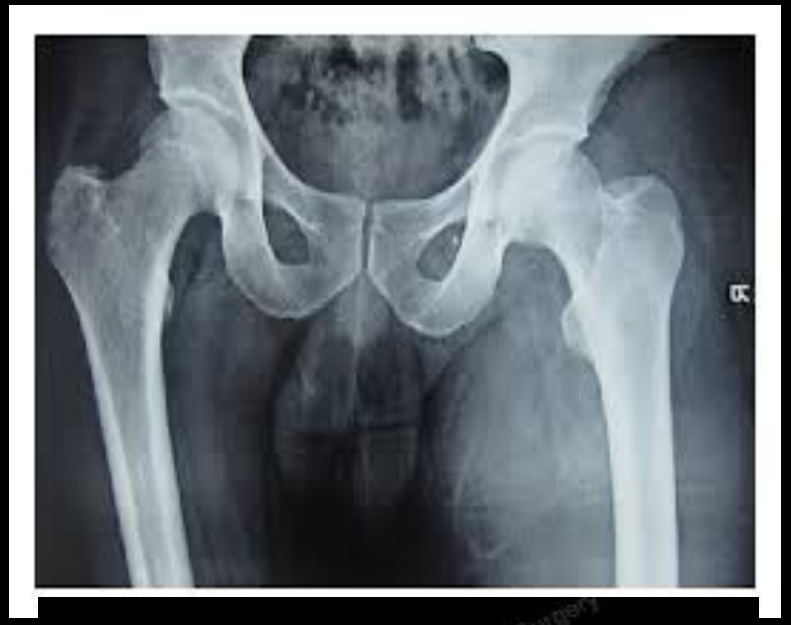
Increasing chondrocyte maturation

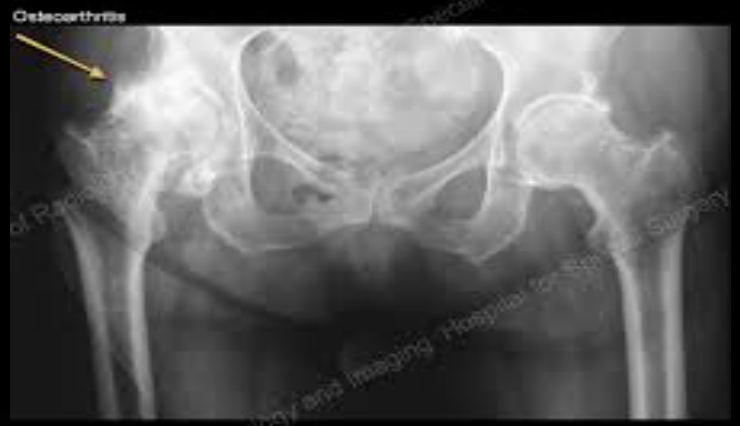
Senolytic

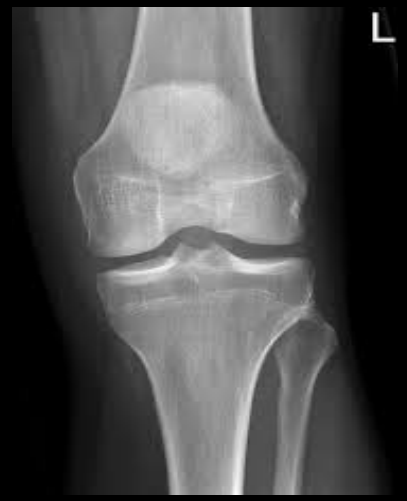
Pain medications: anti-NGF

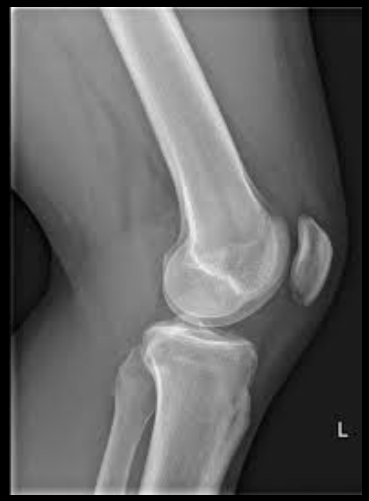
Anti-inflammatory: IL-1B inhibitor

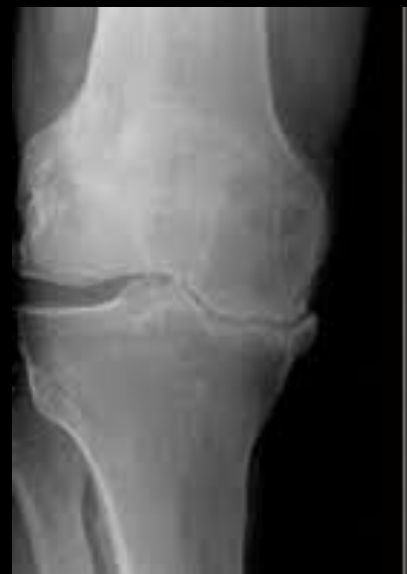
Loss of Cartilage Results in New Bone Formation with Both Knee and Hip Osteoarthritis

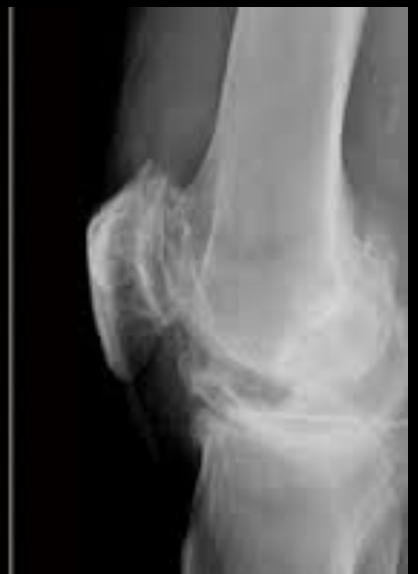






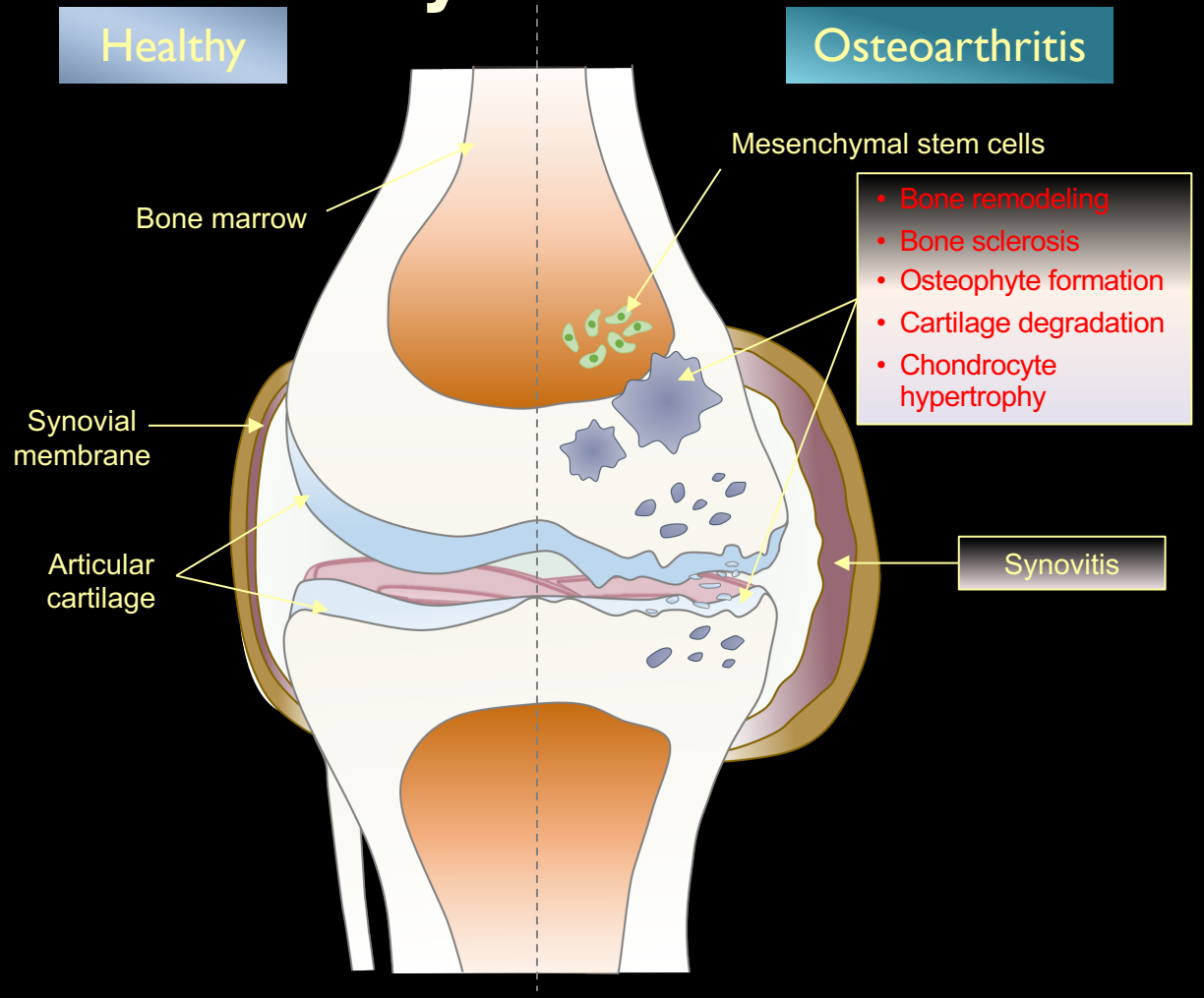






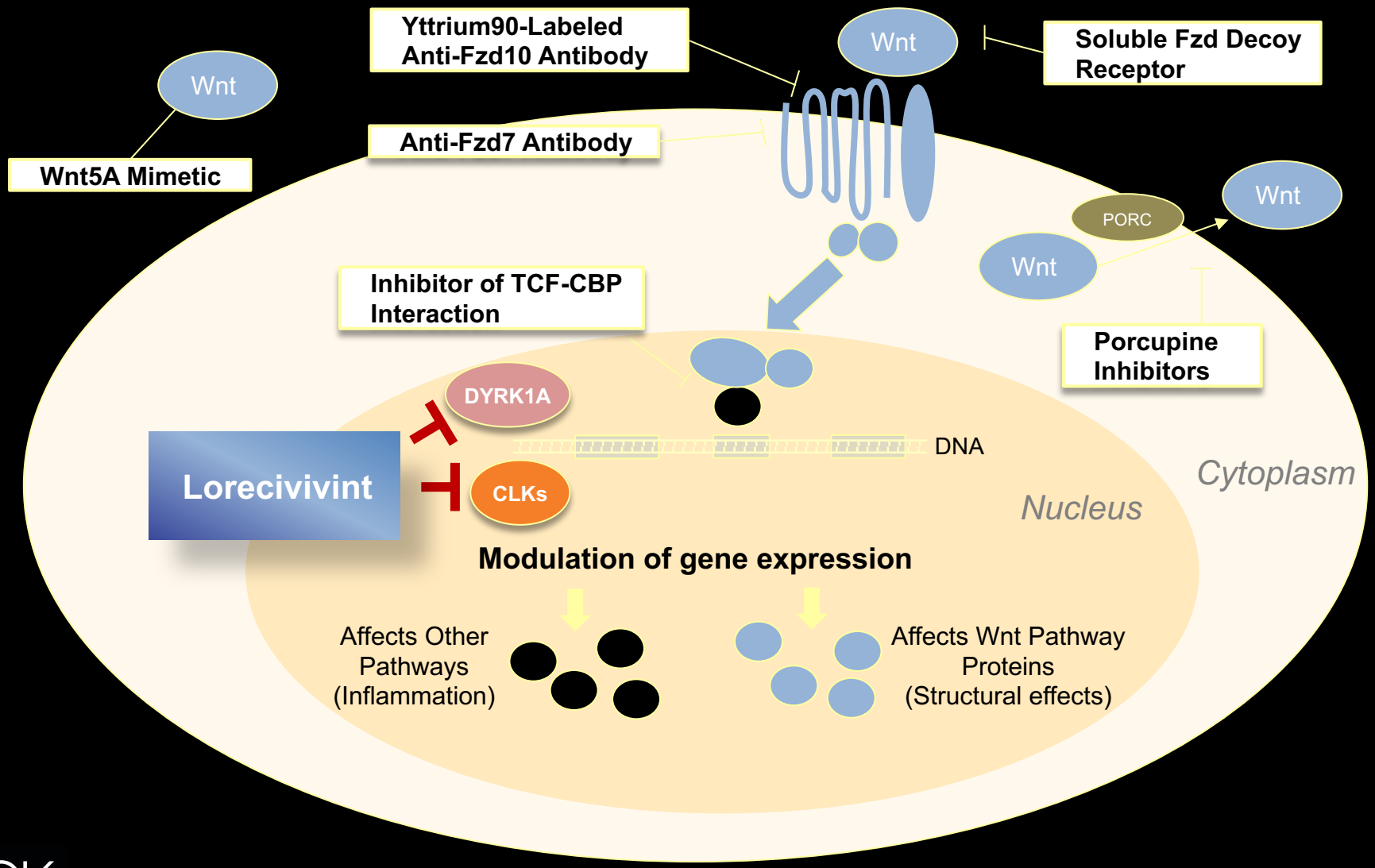
Osteoarthritis (OA) and the Wnt Pathway

- Degenerative tissue remodeling is due to mechanical forces and inflammation[1]
- Overexpressed Wnt proteins and pathway mutations are associated with OA[2-5]
- Increased Wnt signaling drives **bone formation, cartilage breakdown, and inflammation**[6-9]
- **Hypothesis: Inhibiting the Wnt pathway reduces inflammation while protecting and regenerating**

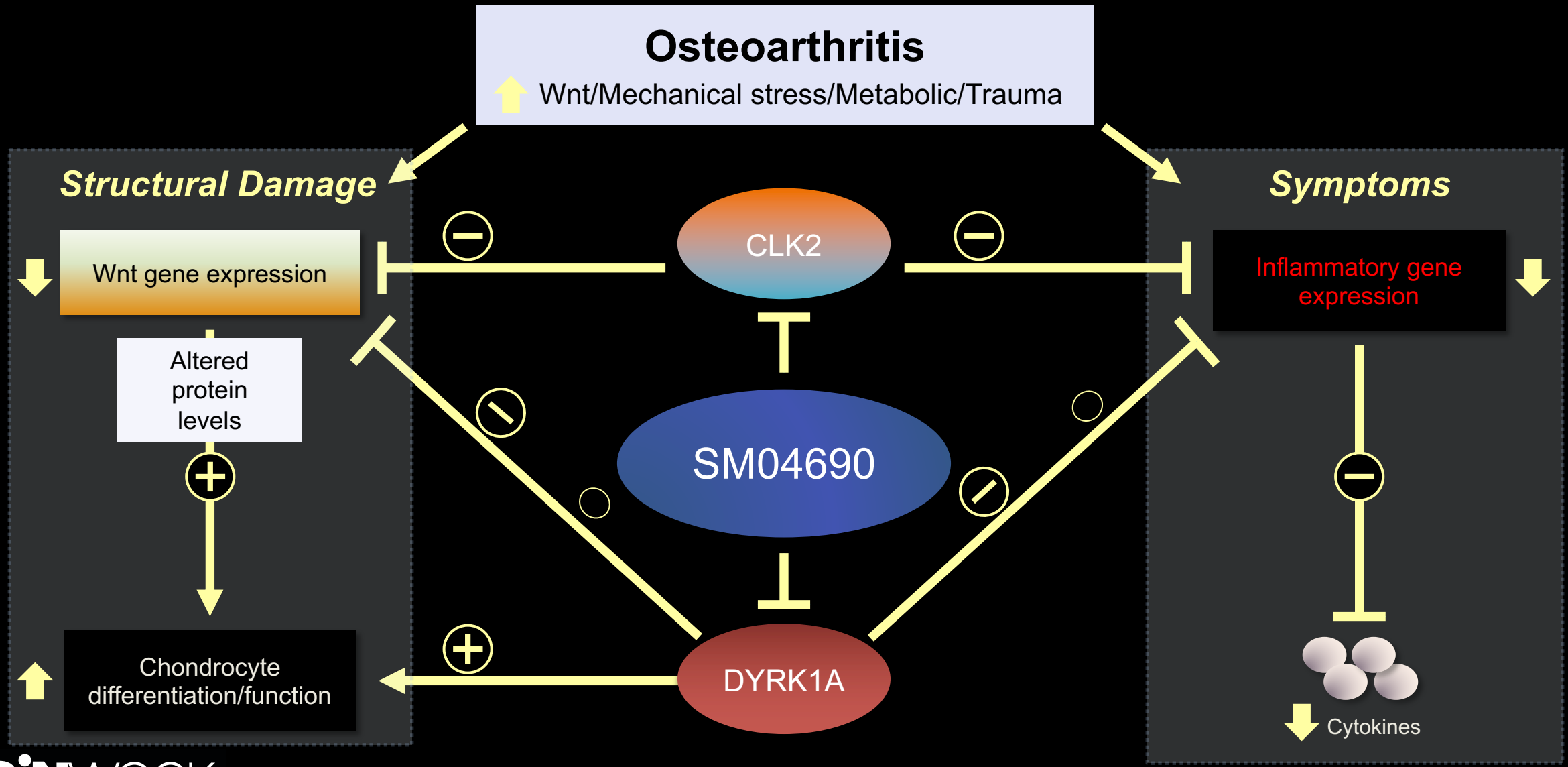


Loeser R. *Arthritis Rheum.* 2006
Hamerman D. *N Engl J Med.* 1993
Yuasa T, et al. *Lab Invest.* 2008
Ma B and Hottiger MO. *Frontiers Immun.* 2016
Sokolove J and Lepus CM. *Ther Adv Musculoskelet Dis.* 2013
6. Blom AB, et al. *Arthritis Rheum.* 2009
7. Monteagudo S, et al. *Nat Commun.* 2017
8. Rudnicki JA and Brown AM. *Dev Biol.* 1997
9. Thomas RS, et al. *Arthritis Res Ther.* 2011

Lorecivivint inhibits the Wnt pathway through a unique MOA



Lorecivivint Mechanism of Action



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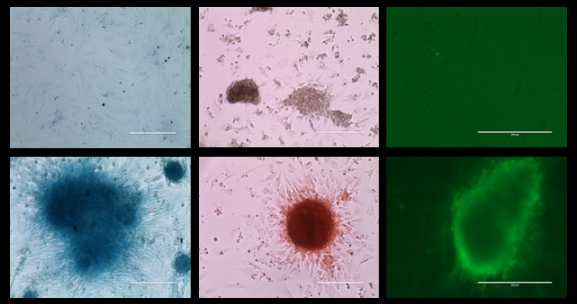
STAT3: signal transducer and activator of transcription 3, SIRT1: sirtuin 1, TCF7: transcription factor 7, NF- B: nuclear factor kappa-light-chain-enhancer of activated B cells, FOXO1: forkhead Box O1

Lorecivivint (LOR; SM04690) Preclinical Development

***In vitro* assays and animal models**

hMSC assays → **Chondrocyte Regeneration**



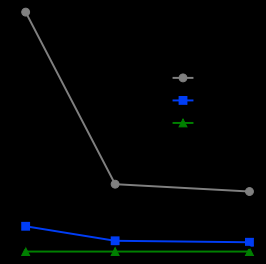
Protease assays → **Cartilage Protection**

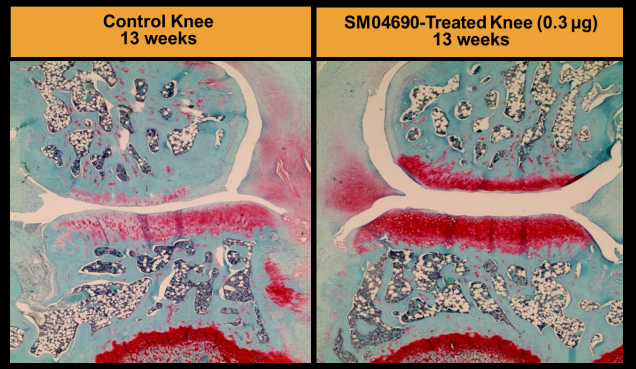
Protease gene expression

Cytokine assays → **Anti-inflammation**

Cytokine gene expression

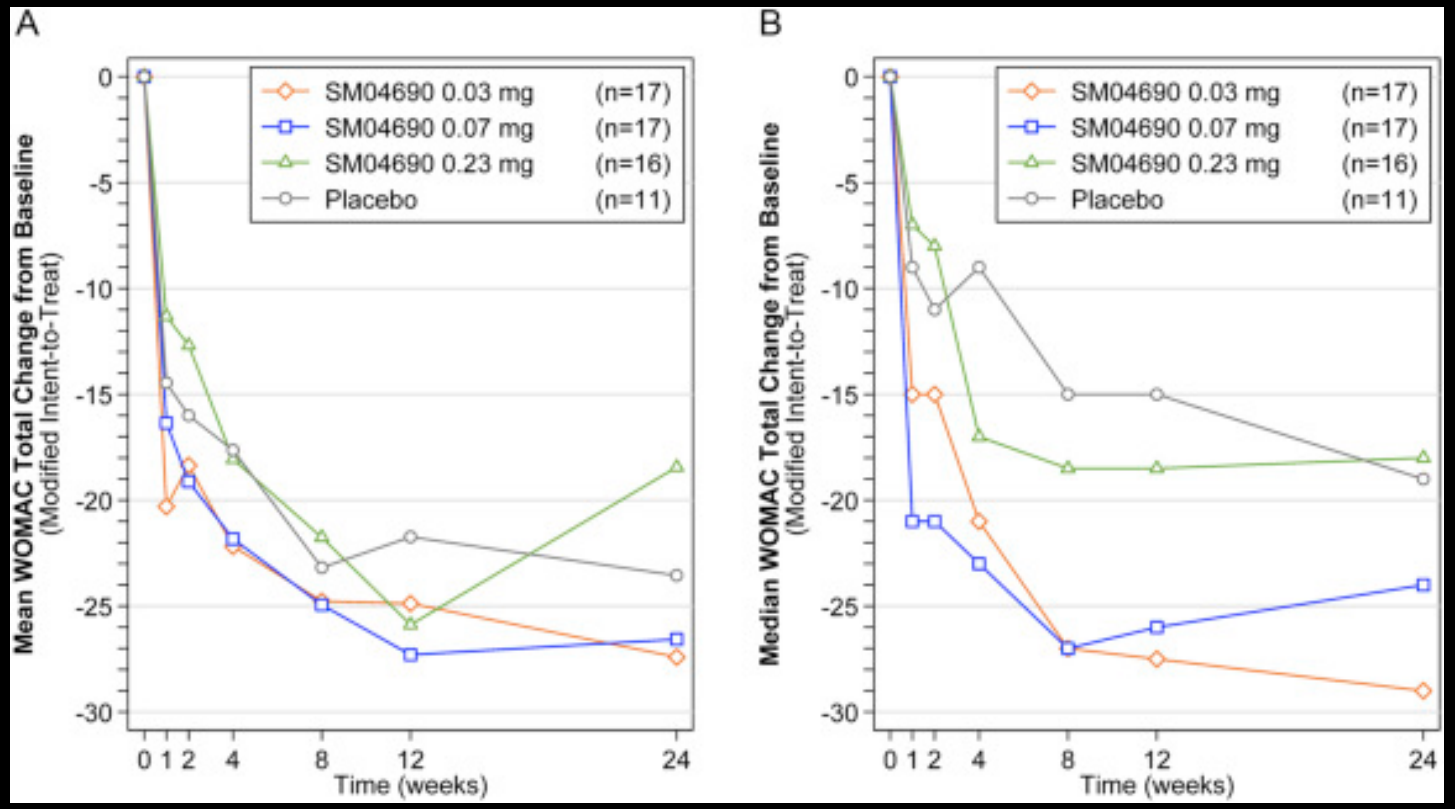
Animal models → **Sustained Local PK**





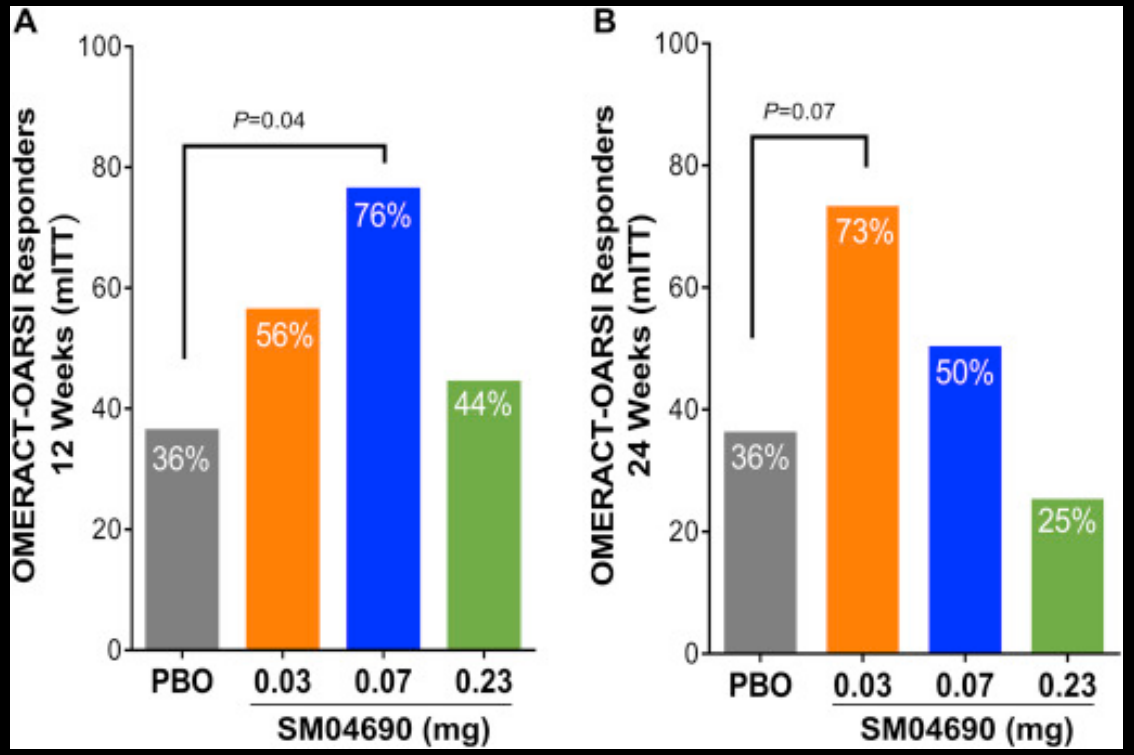
Improved Joint Health
(Animal models)

Phase Ib study of Wnt Pathway Inbibitor for the Treatment of Painful Knee OA



Yazici Y, et al. Osteoarthritis and Cartilage. 2017.

Percent of OMERACT-OARSI Responders at Weeks 12 and 24

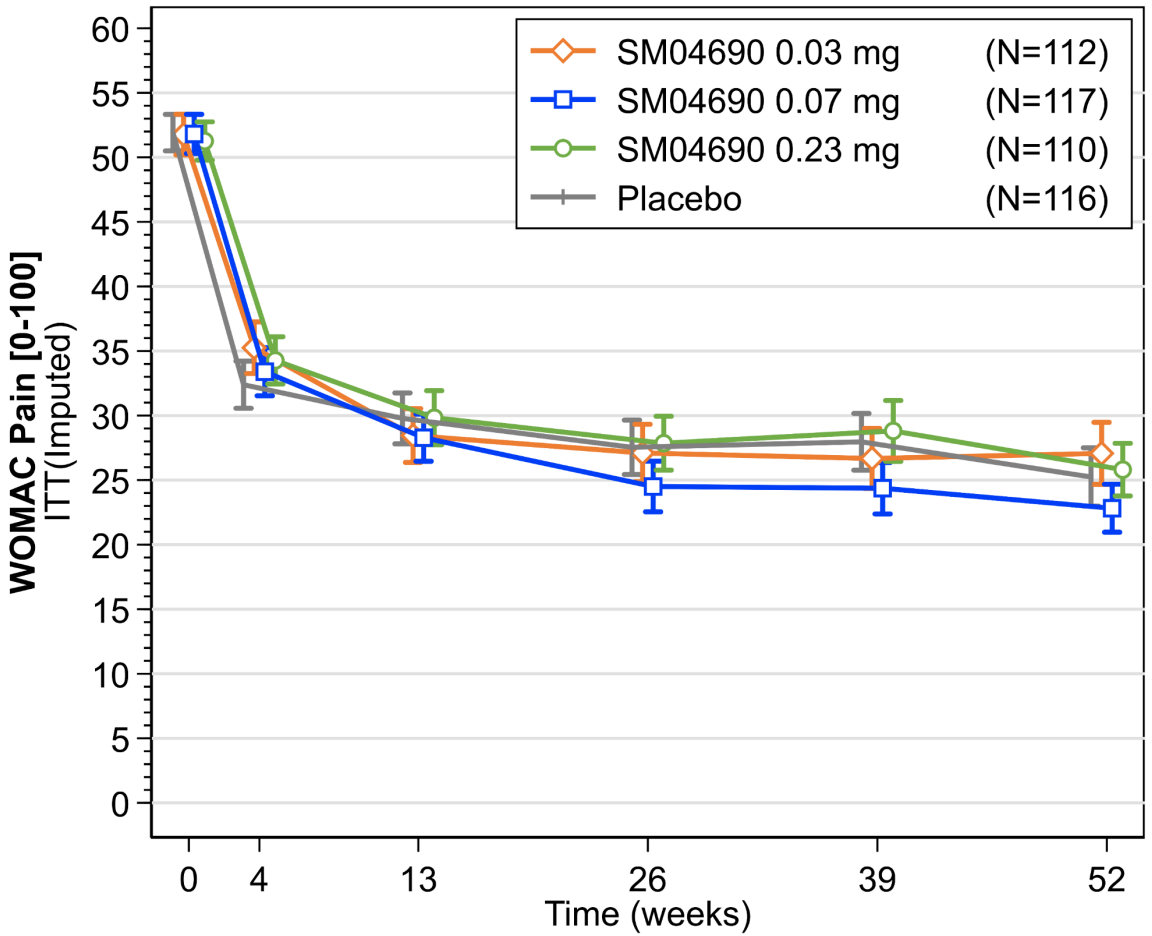


Yazici Y, et al. Osteoarthritis and Cartilage 2017; 1598-1606

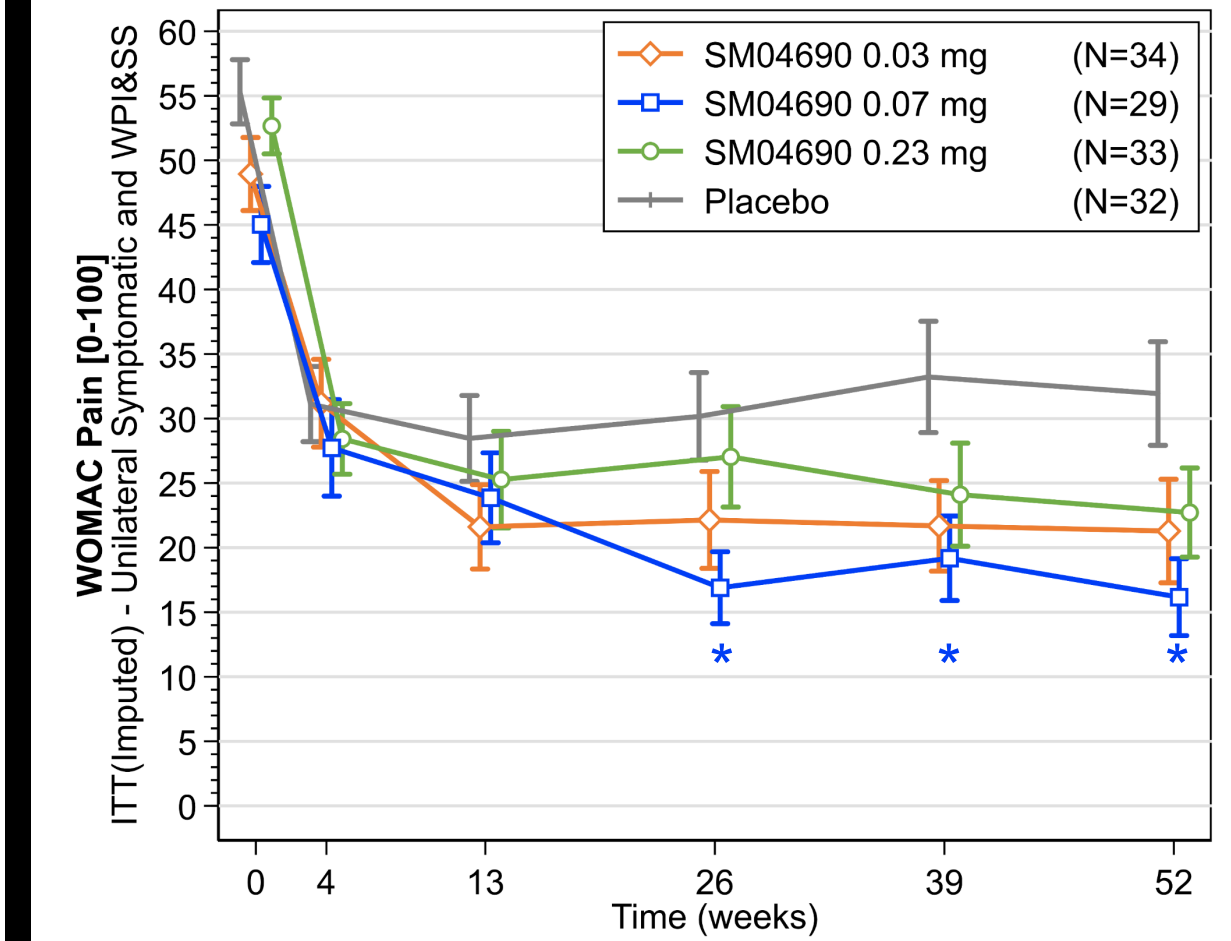
LOR (SM04690) – WOMAC Knee Pain [0-100]

Actual scores (mean ± standard errors)

Intention-To-Treat



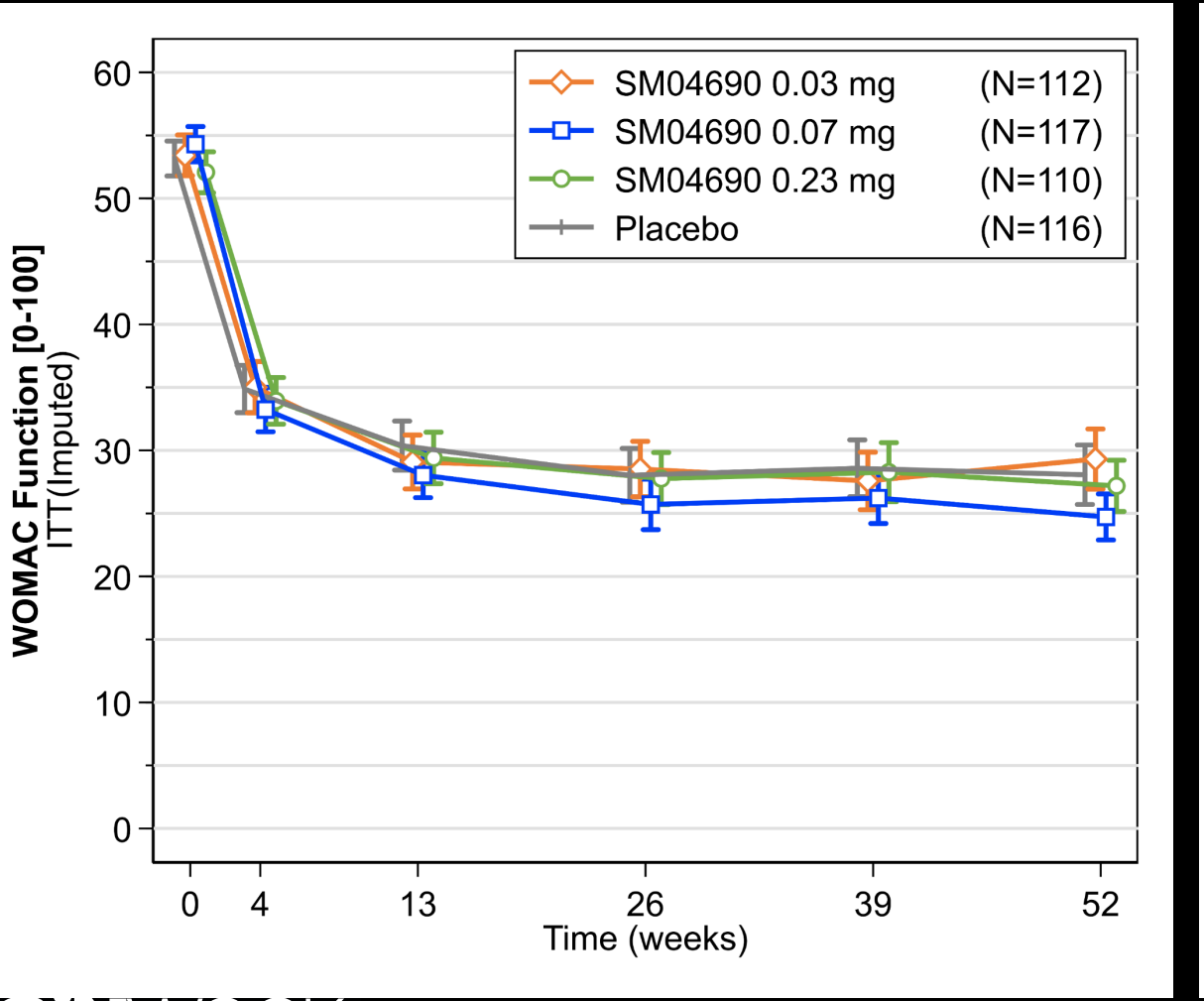
Unilateral Symptomatic Without Widespread Pain



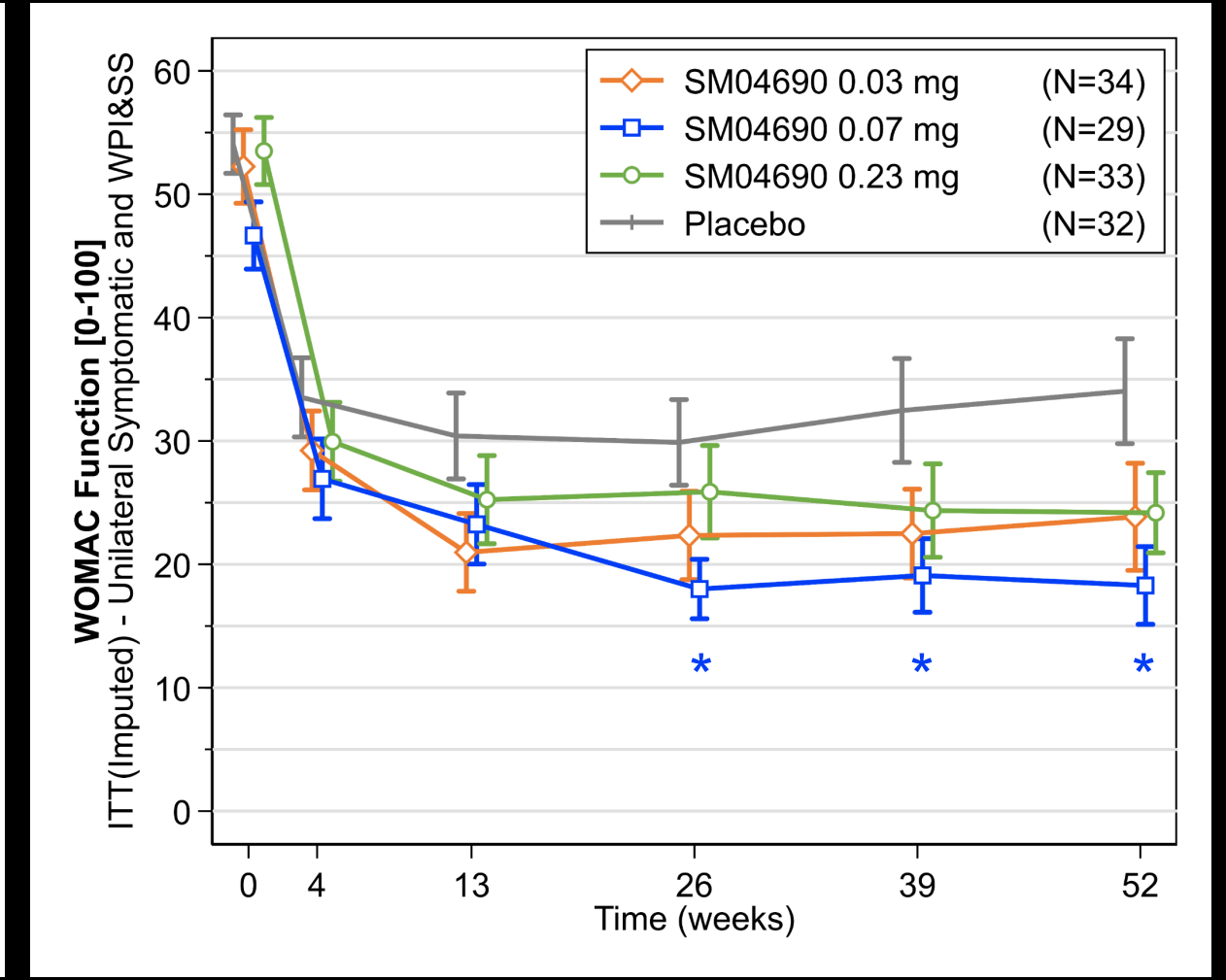
LOR (SM04690) - WOMAC Function [0-100]

Actual scores (mean ± standard errors)

Intention-To-Treat



Unilateral Symptomatic Without Widespread Pain

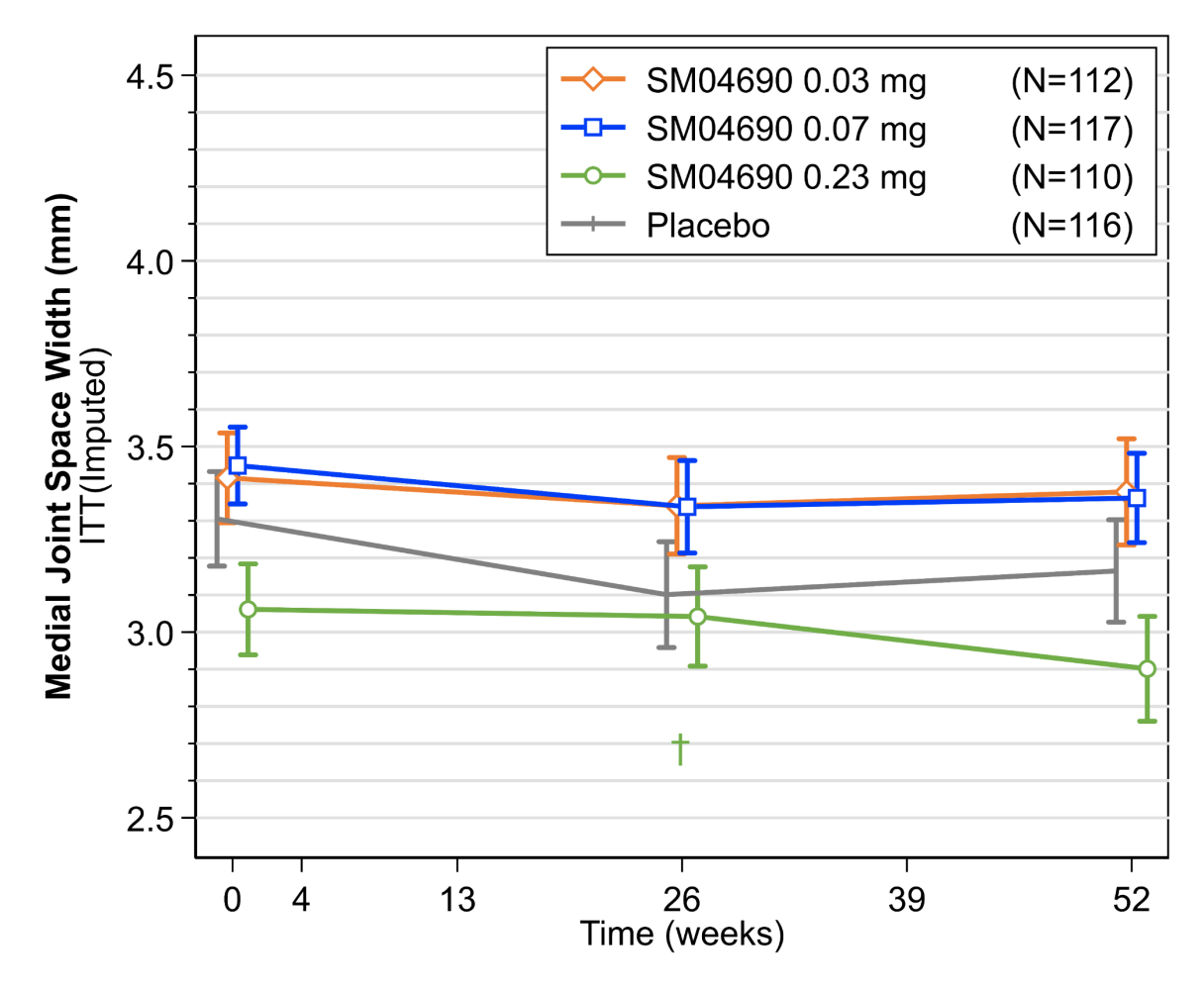


*SM04690 0.07 mg $P<0.05$

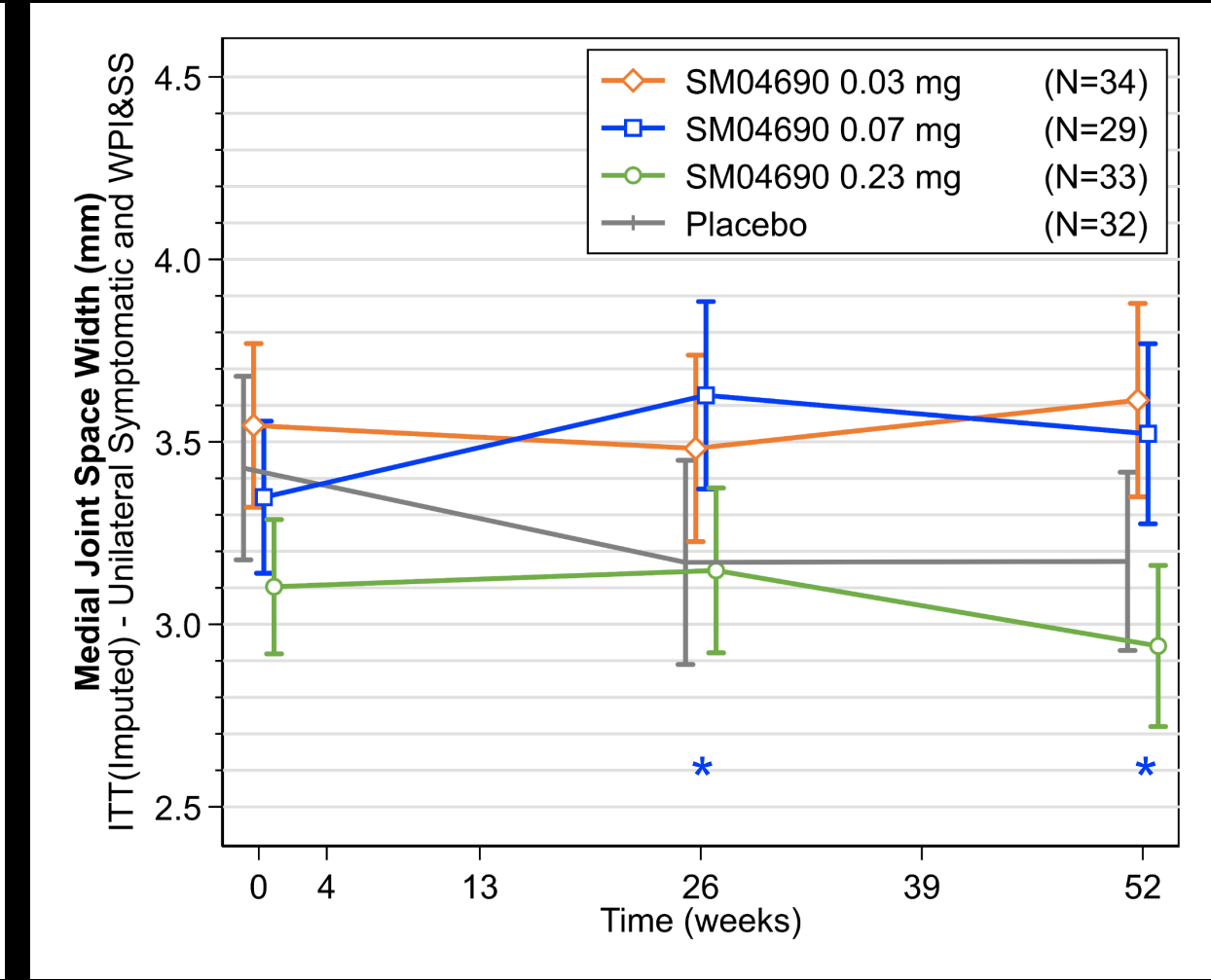
LOR (SM04690) - Medial Joint Space Width (mJSW)

Actual scores (mean ± standard errors)

Intention-To-Treat



Unilateral Symptomatic Without Widespread Pain



Lorecivivint Phase 2b Clinical Data

LOR Phase 2b: Subject Characteristics
Full analysis set

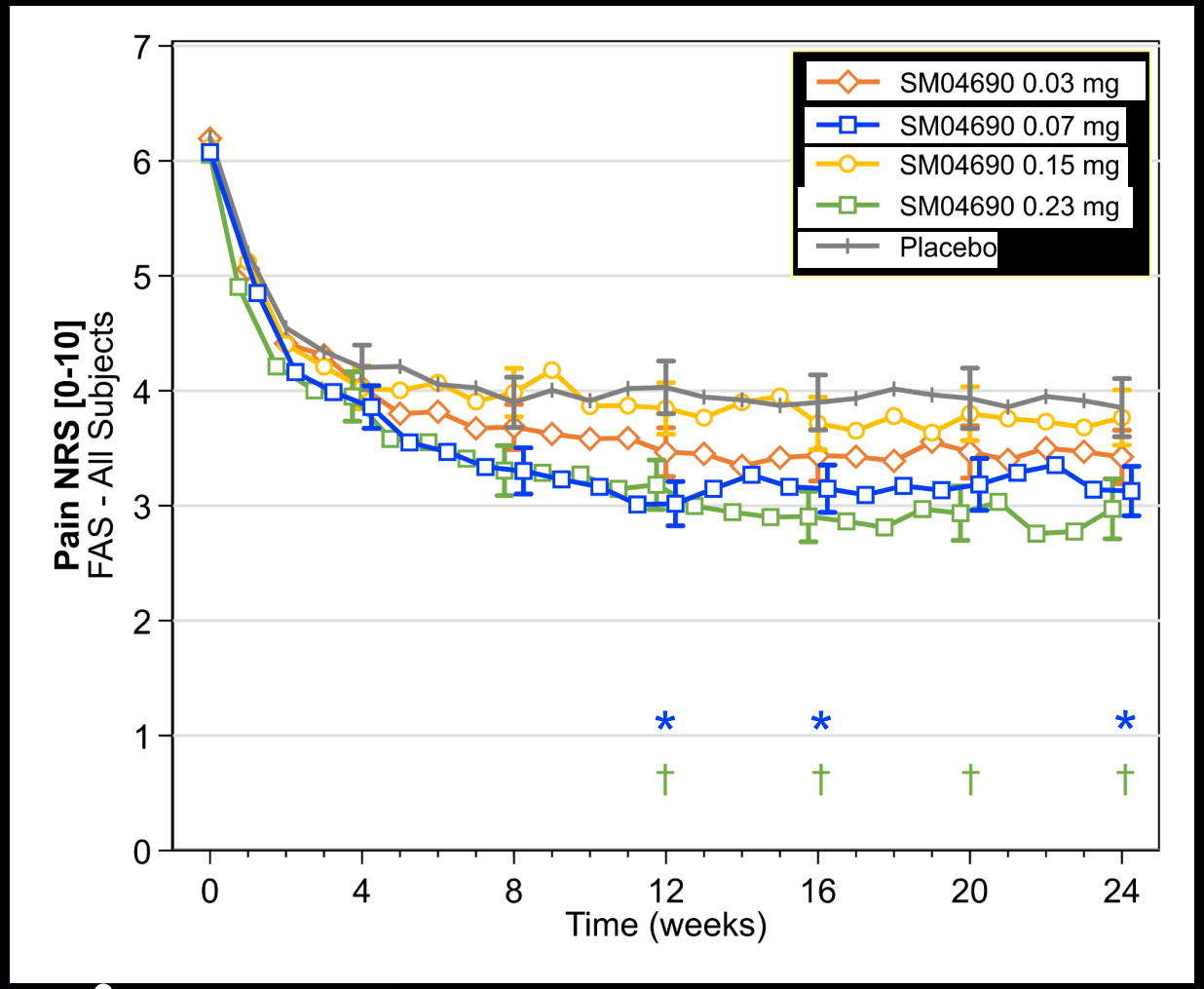
	Lorecivivint				
	0.03 mg	0.07 mg	0.15 mg	0.23 mg	Placebo
N	116	115	115	116	116
Age at Consent (years)*	57.9 (7.9)	59.9 (8.6)	58.4 (8.3)	58.5 (9.0)	60.1 (9.0)
BMI (kg/m^2)*	29.2 (3.8)	29.1 (3.6)	29.4 (4.1)	28.5 (4.4)	28.6 (4.3)
Female	76 (65.5%)	66 (57.4%)	69 (60.0%)	61 (52.6%)	64 (55.2%)
Race					
White	85 (73.3%)	83 (72.2%)	84 (73.0%)	89 (76.7%)	90 (77.6%)
African American	24 (20.7%)	22 (19.1%)	25 (21.7%)	21 (18.1%)	17 (14.7%)
Asian	5 (4.3%)	5 (4.3%)	6 (5.2%)	5 (4.3%)	6 (5.2%)
KL Grade 3	63 (54.3%)	74 (64.3%)	68 (59.1%)	63 (54.3%)	72 (62.1%)
Unilateral Symptomatic†	59 (50.9%)	62 (53.9%)	63 (54.8%)	63 (54.3%)	61 (52.6%)
Widespread Pain Negative††	92 (79.3%)	93 (80.9%)	90 (78.3%)	93 (80.2%)	93 (80.2%)

*Mean (SD) reported. Otherwise N (%) reported
† Unilateral symptomatic vs. bilateral symptomatic stratified to 50% each
†† Widespread Pain Negative (WPI ≤4 and Symptom Severity score ≤2) stratified to 80% of population

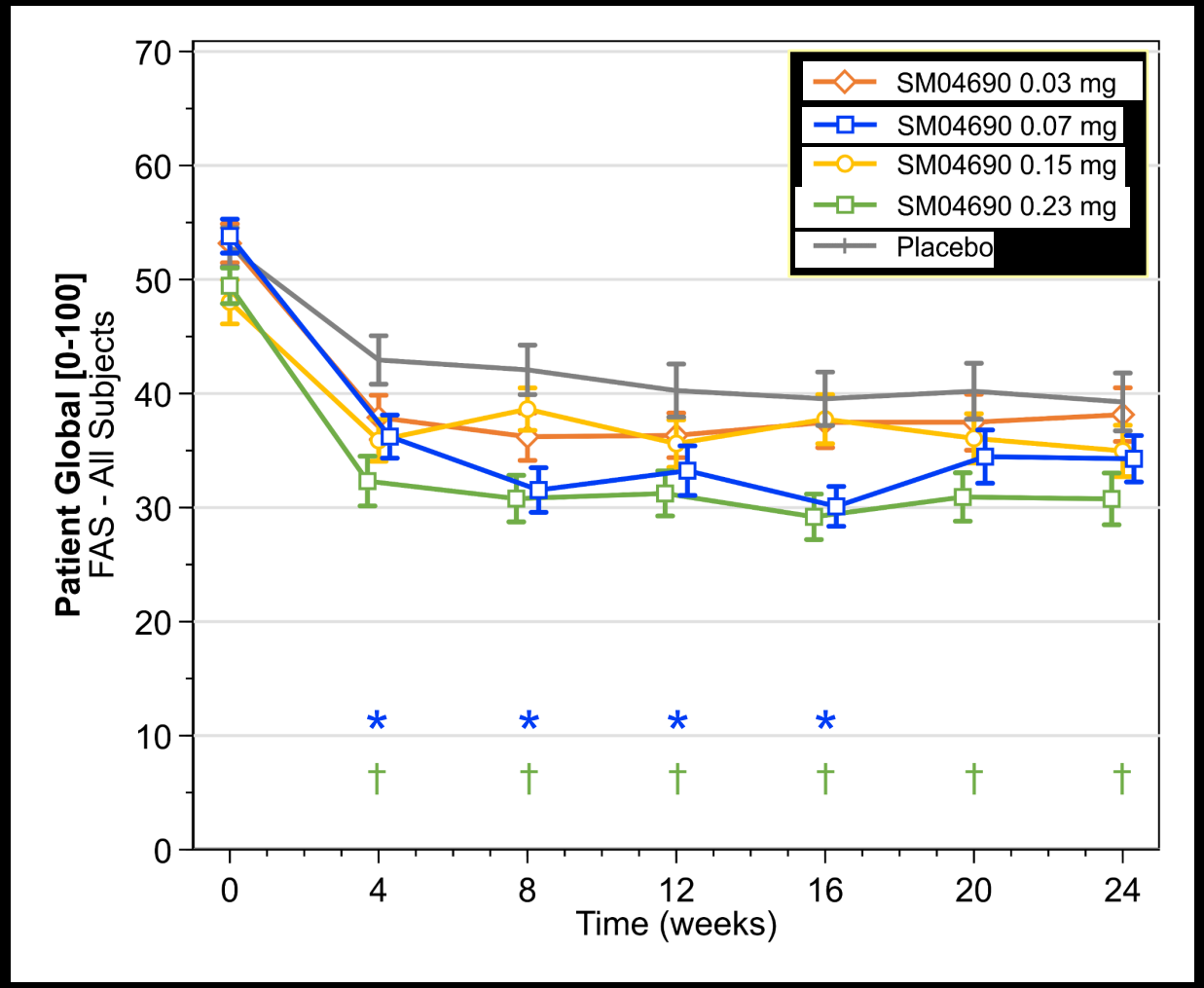
LOR (SM04690) – Pain NRS [0-10], Patient Global [0-100]

Actual scores (mean ± standard errors)

Pain NRS (FAS)



Patient Global (FAS)

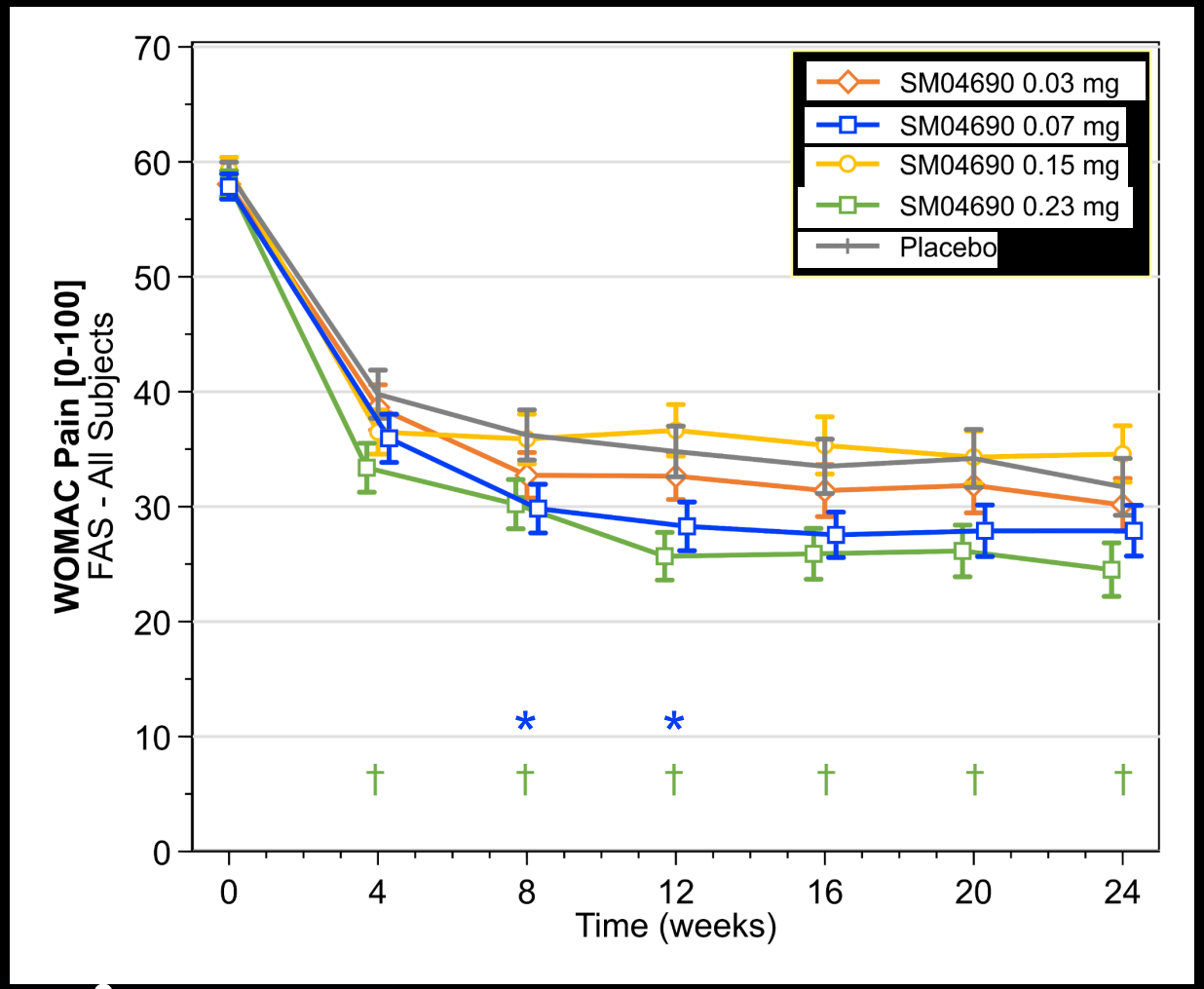


Comparisons of LOR vs. PBO using a baseline-adjusted ANCOVA. Data on x-axis is offset for visual clarity.

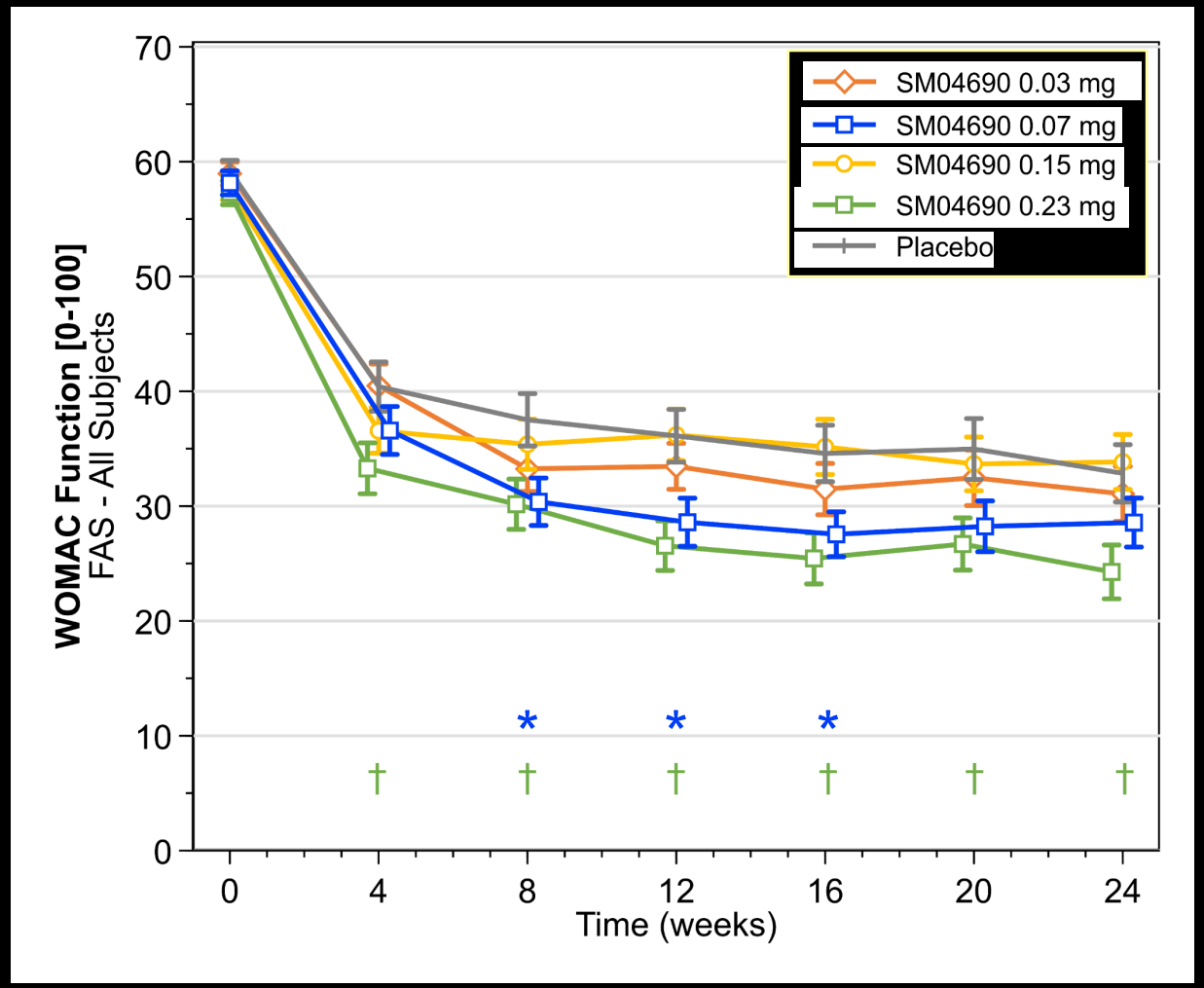
*SM04690 0.07 mg $P<0.05$ †SM04690 0.23 mg $P<0.05$

LOR (SM04690) – WOMAC Pain [0-100], Function [0-100]

WOMAC Pain (FAS)



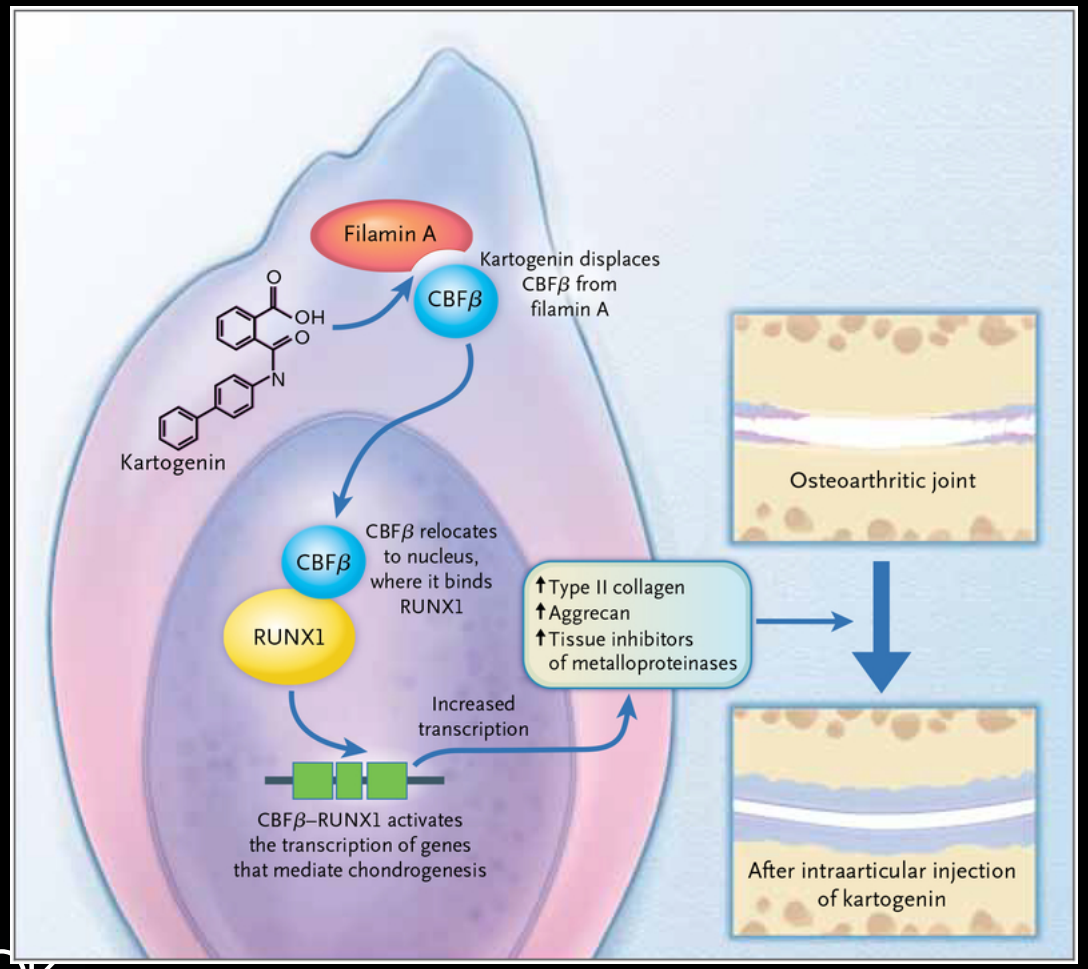
WOMAC Function (FAS)



Comparisons of LOR vs. PBO using a baseline-adjusted ANCOVA. Data on x-axis is offset for visual clarity.
*SM04690 0.07 mg *P*<0.05 †SM04690 0.23 mg *P*<0.05

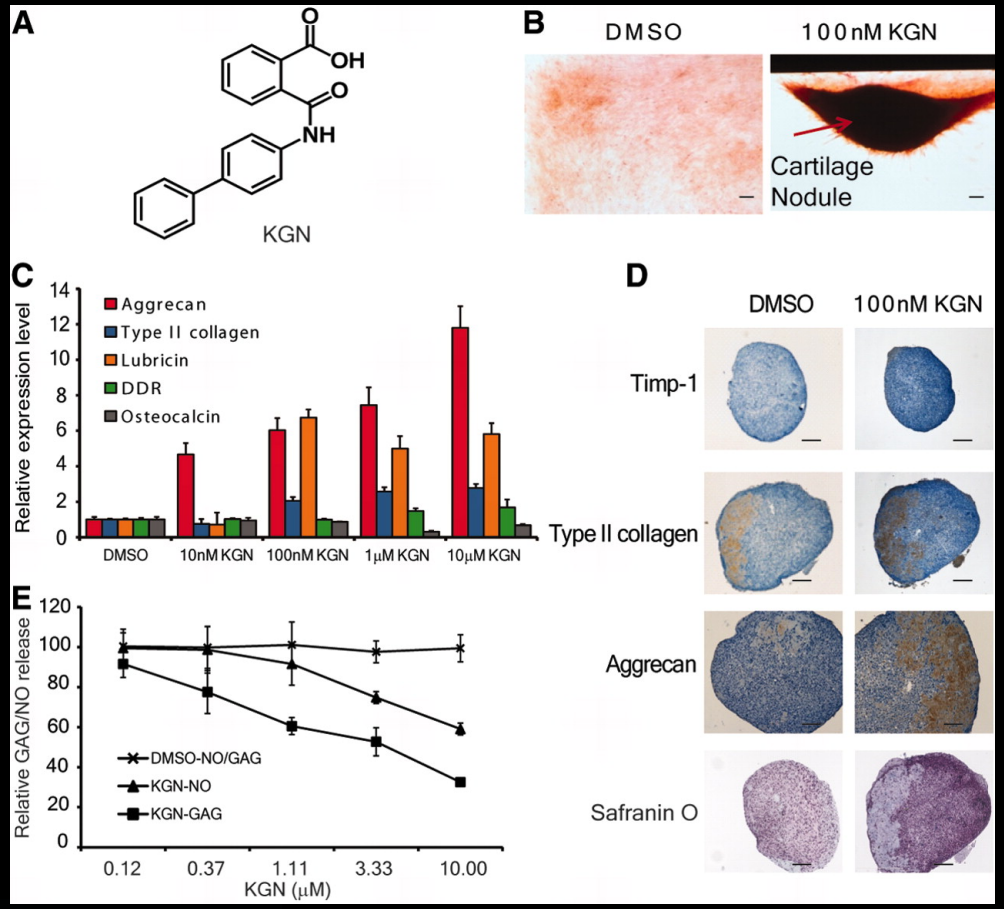
Studies to direct MSCs to differentiate into chondrocytes in the joint.

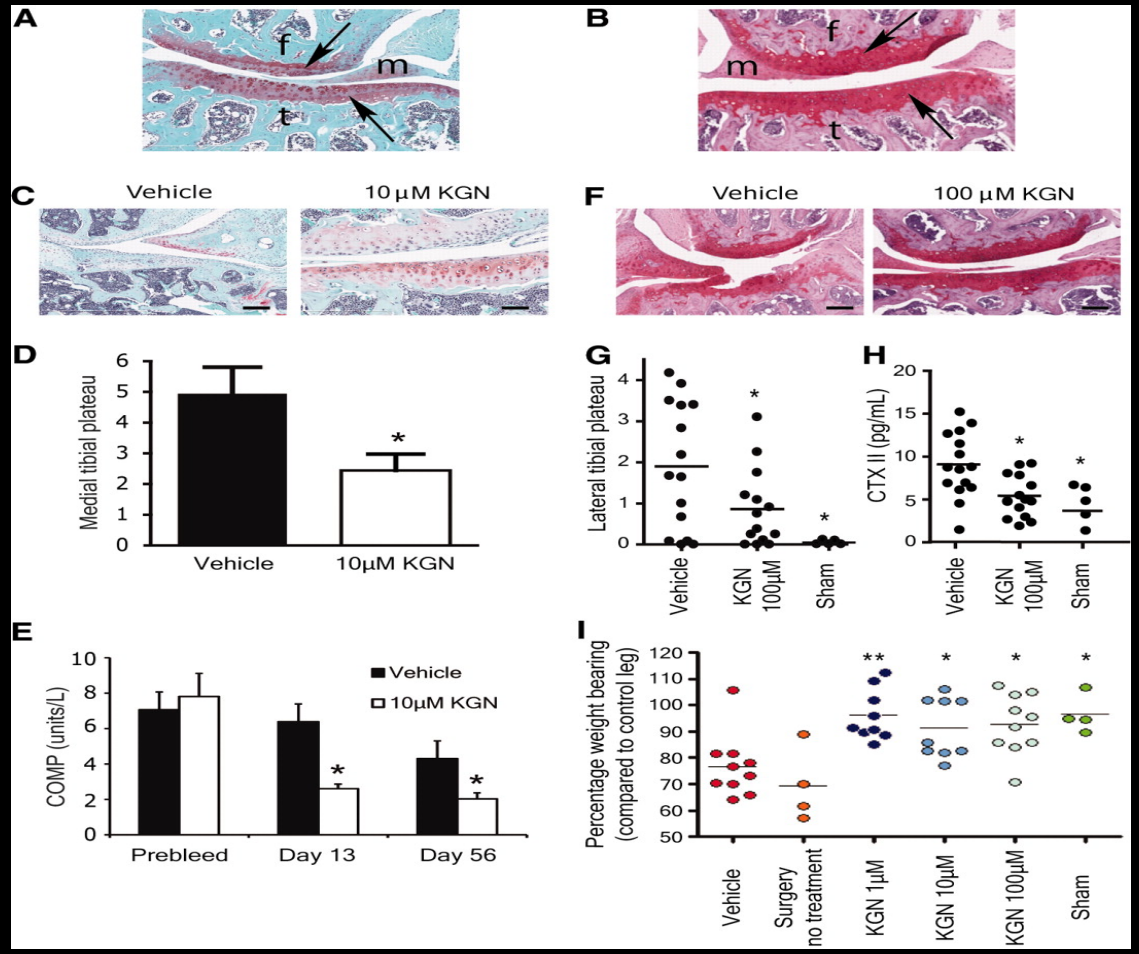
Kartogenin: Differentiates endogenous mesenchymal stem cells into cartilage-producing chondrocytes in vitro



NEJM 2012; 366:2522-2524

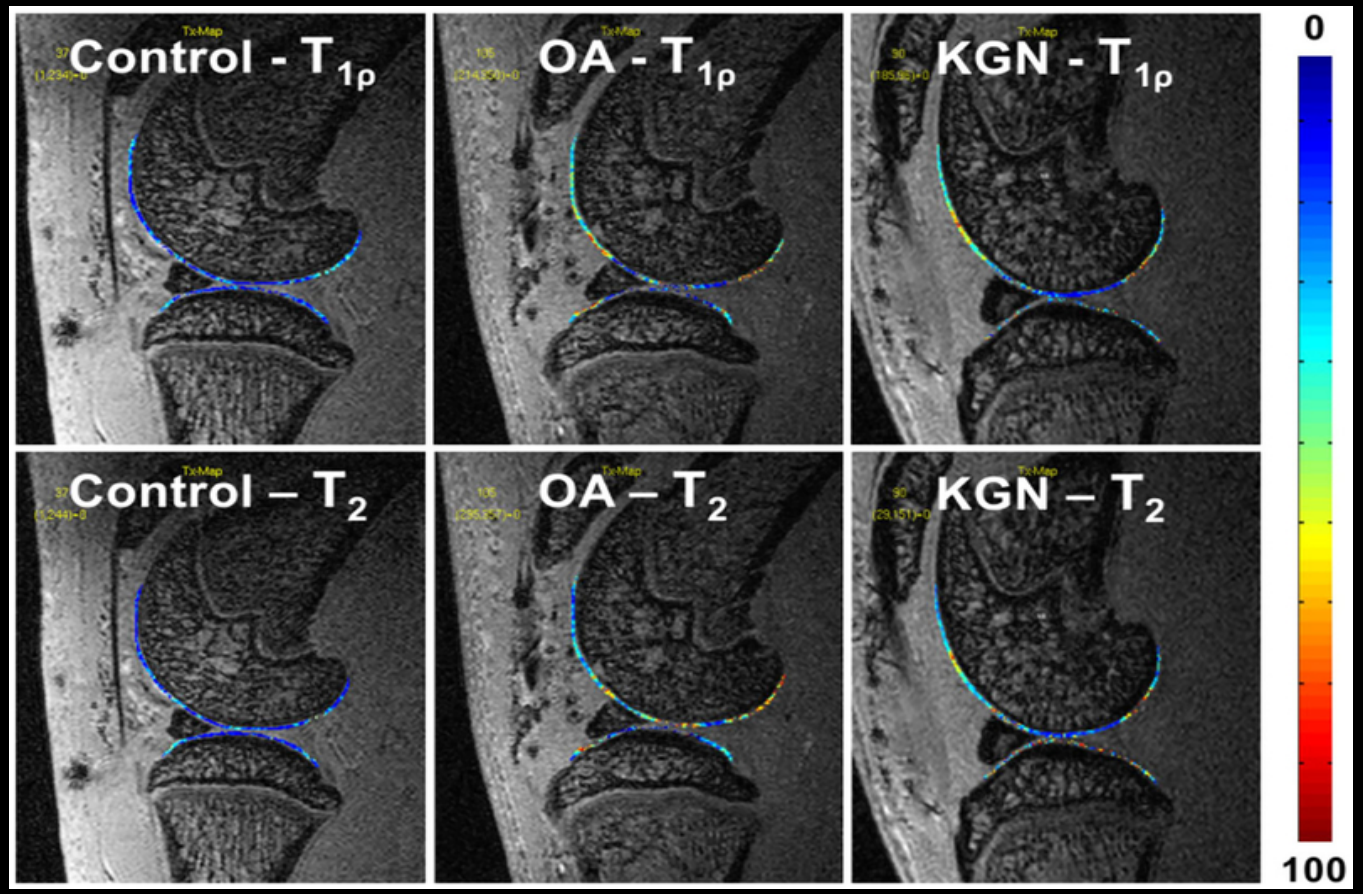
Kartogenin induced chondrocyte differentiation and promoted repair in Collagen-VII induced and surgery induced OA models.





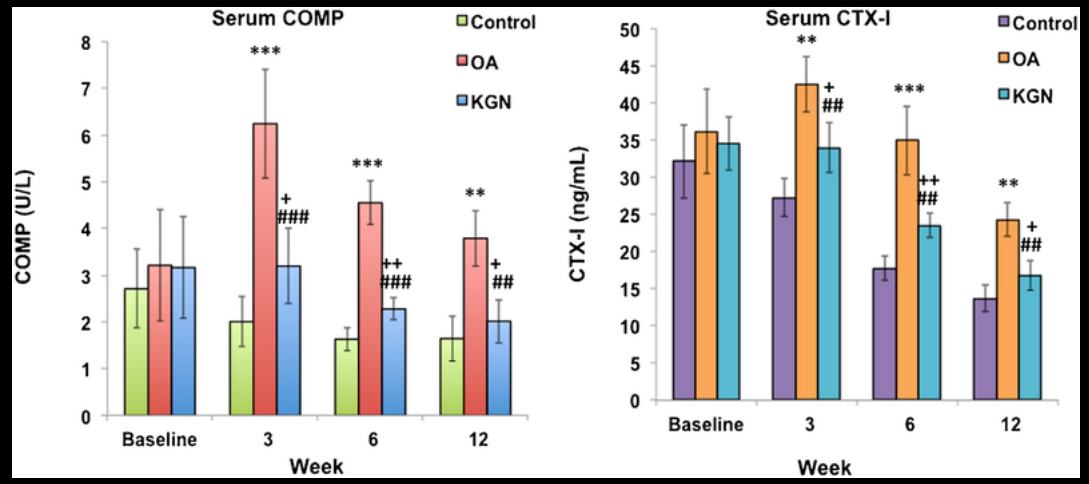
Johnson et al, Science 2012

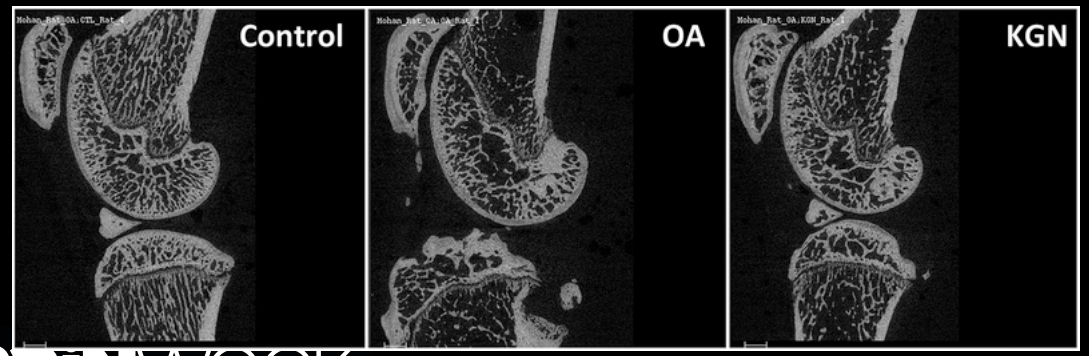
Treatment with Intra-articular Kartogenin for acute Post-traumatic knee OA in rats. Representative articular cartilage $T_{1\rho}$ and T_2 maps of sham-operated control knee joint,

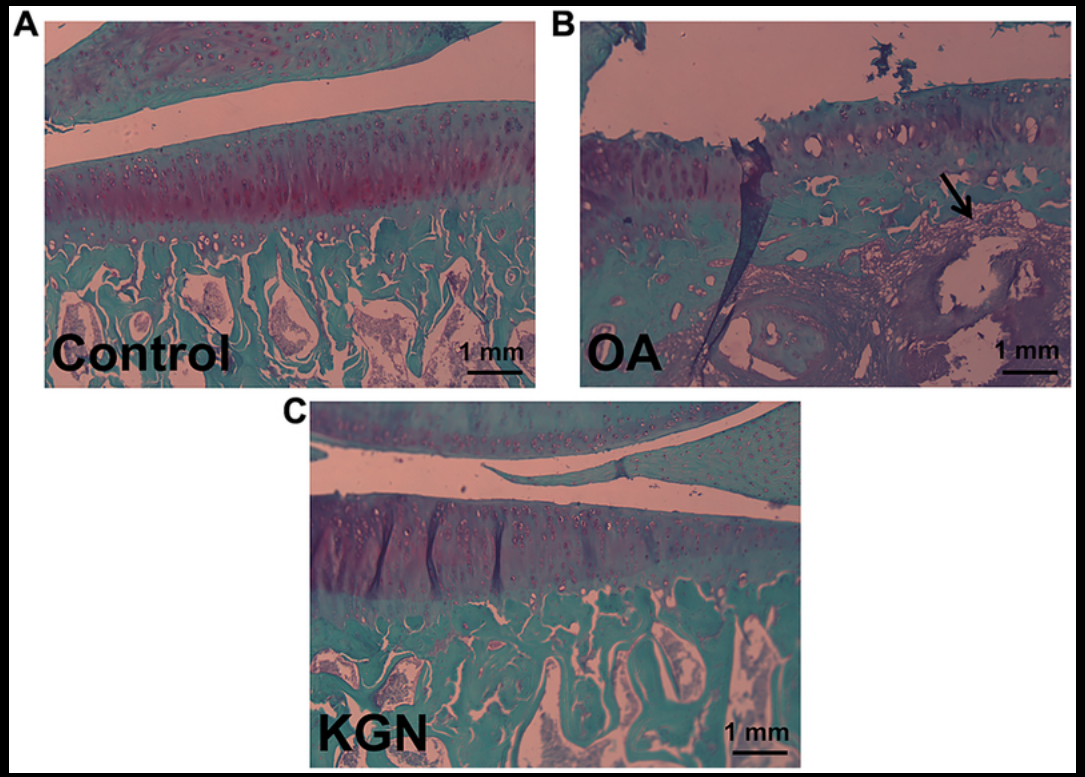


Mohan et al,JJ Orthop Res . 2016 Oct;34(10):1780-1789

Histologic, Imaging and Biochemical outcomes of Kartogenin treatment of rats.



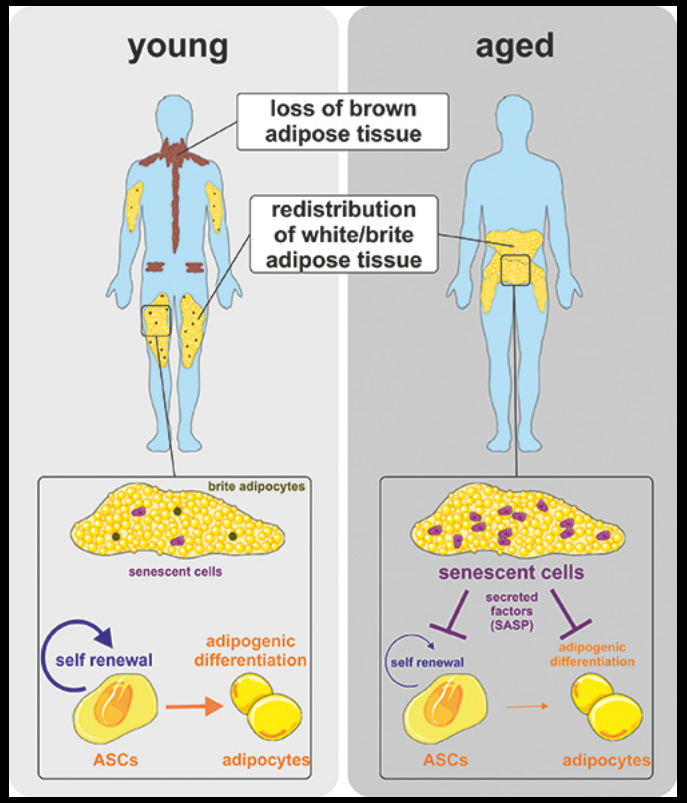


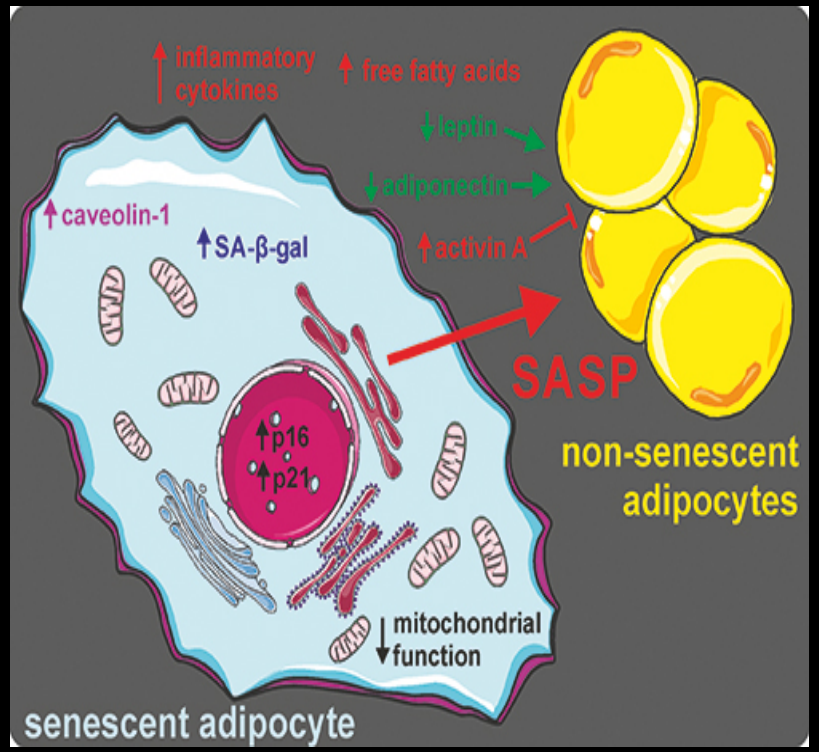


Mohan et al JOR. 2012

Kartogenin is currently in a phase 1b clinical trial for the Treatment of knee OA

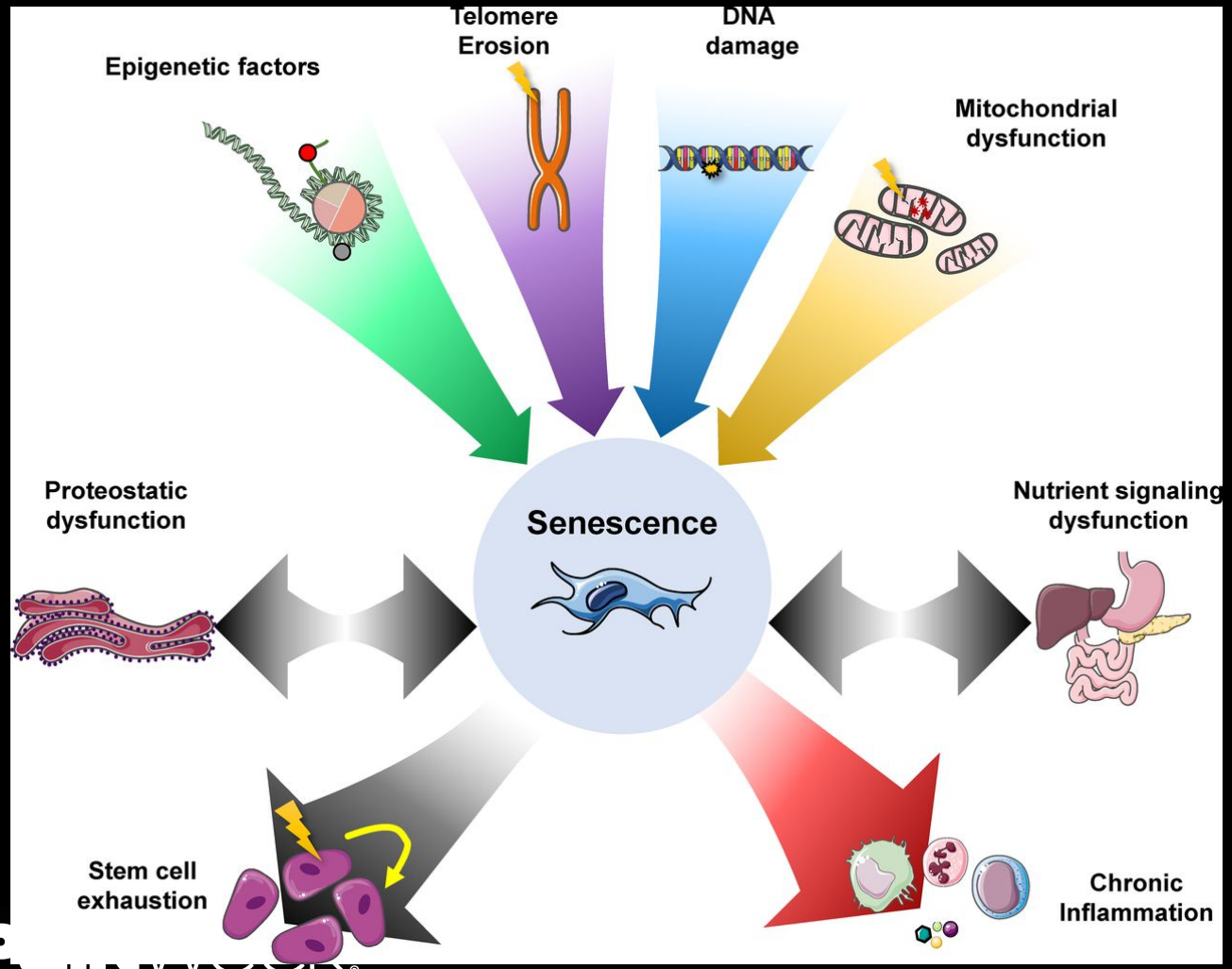
Senescence

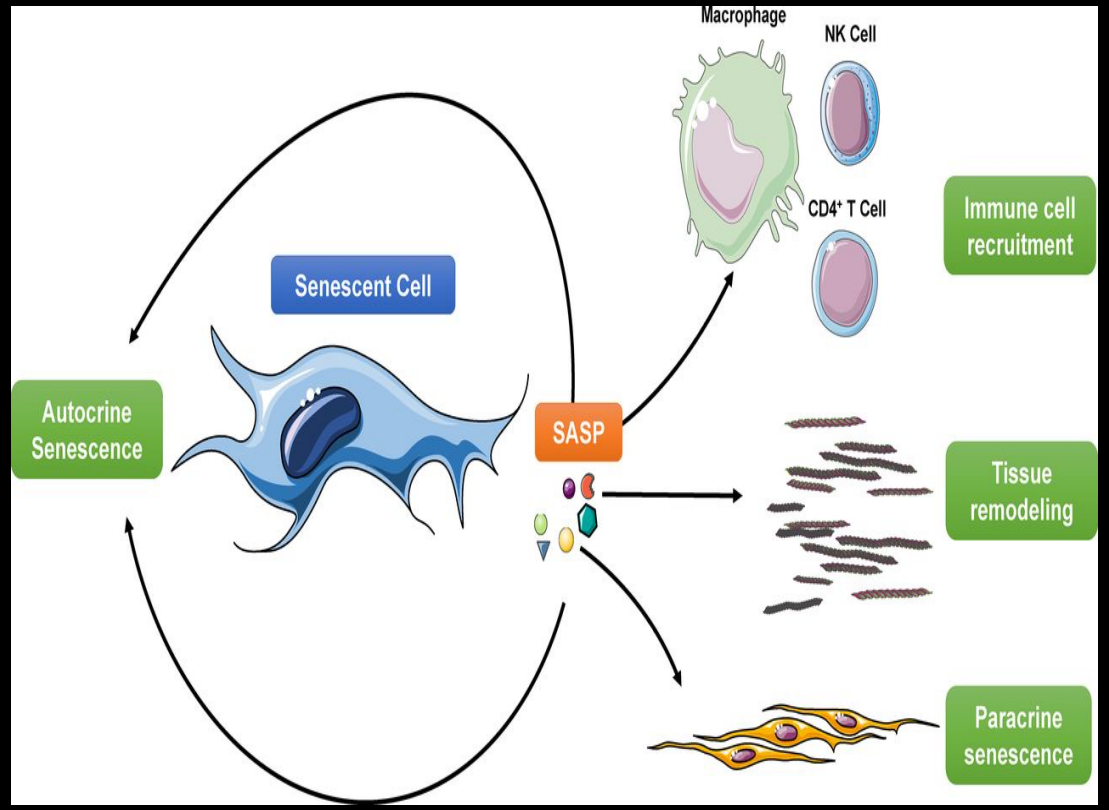




Schosserer M. et al Geromtology. 2018 ·

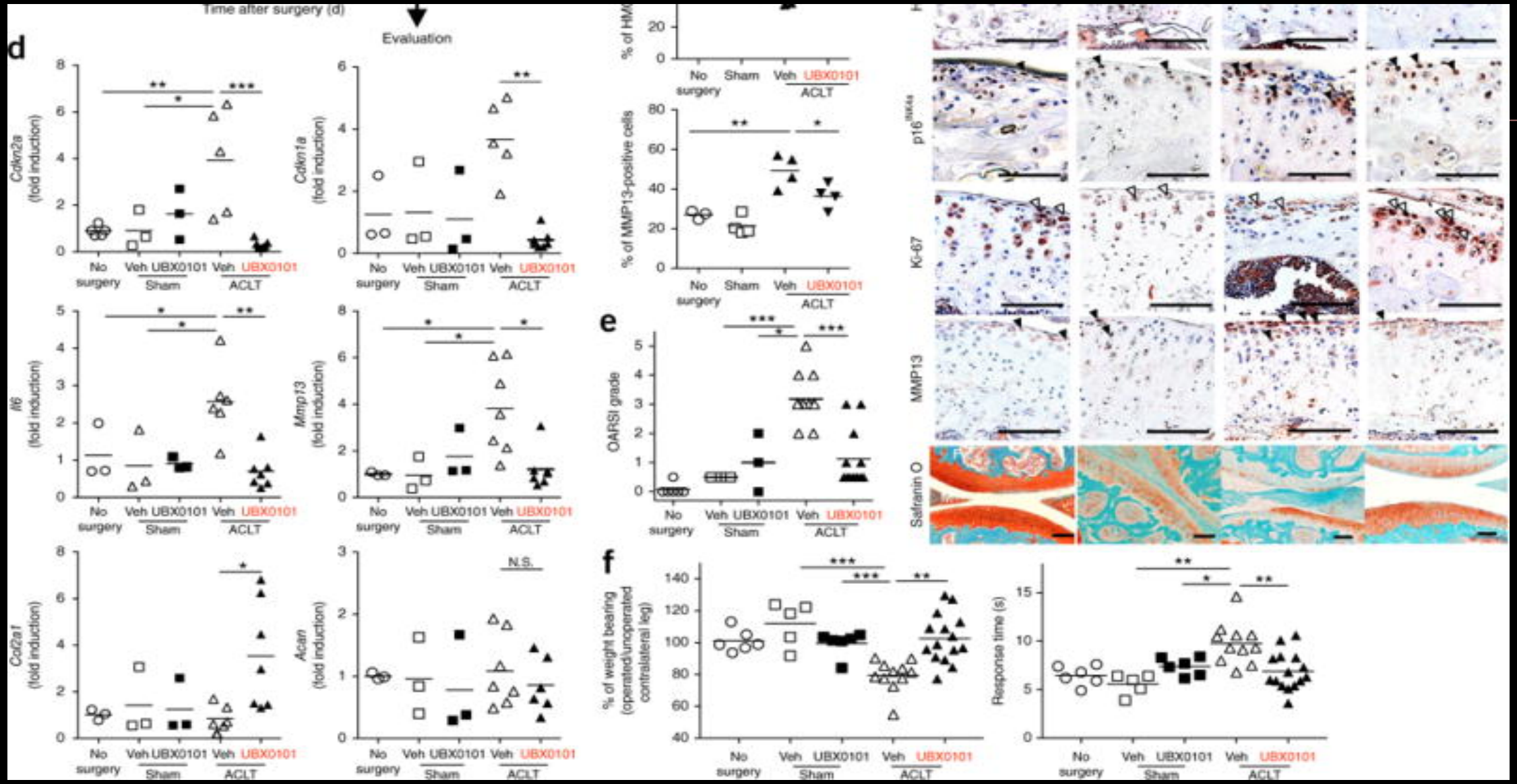
Senescence of cells and the SASP that they release





McHugh et al JBC. 2018

The effects of a senolytic medication on a preclinical model of post-traumatic knee OA



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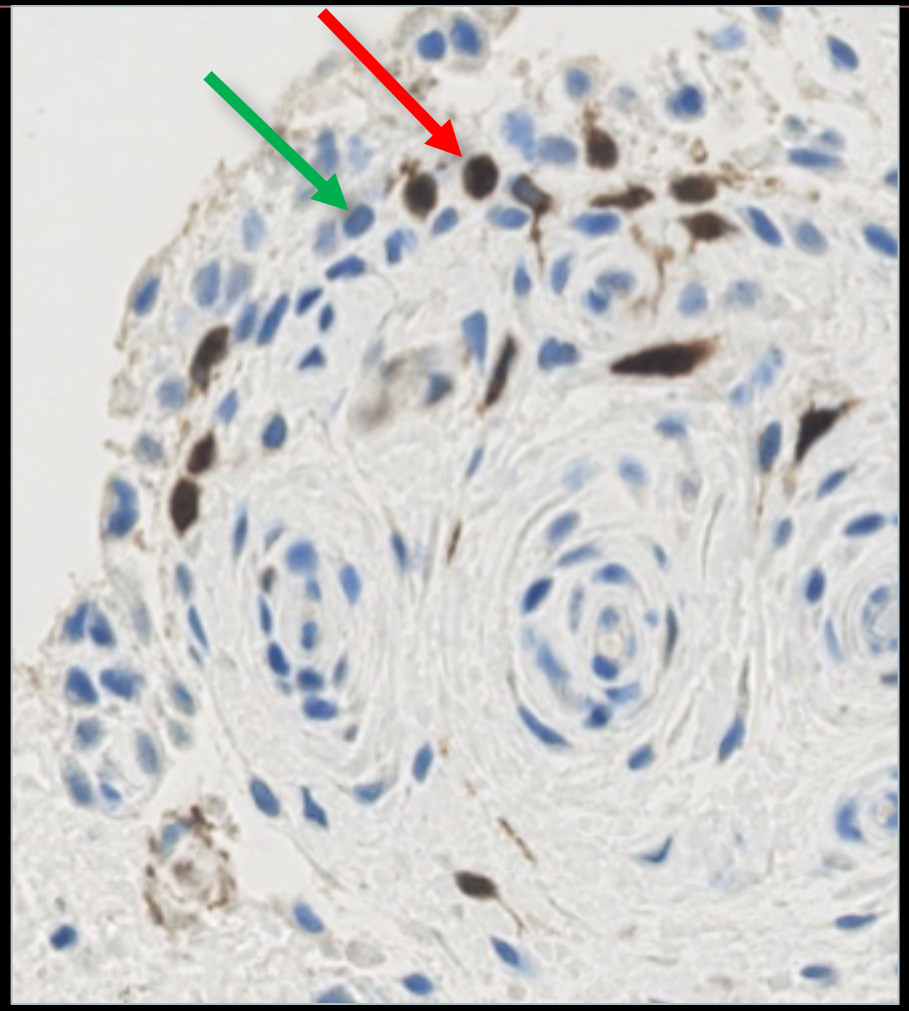
Ok Hee Jeon, et al Nat Med. 2017 Jun; 23(6): 775–781.

INCREASED Senescent cells OBSERVED Synovium in Fibroblasts in from the Knees of OA subjects undergoing arthroscopy



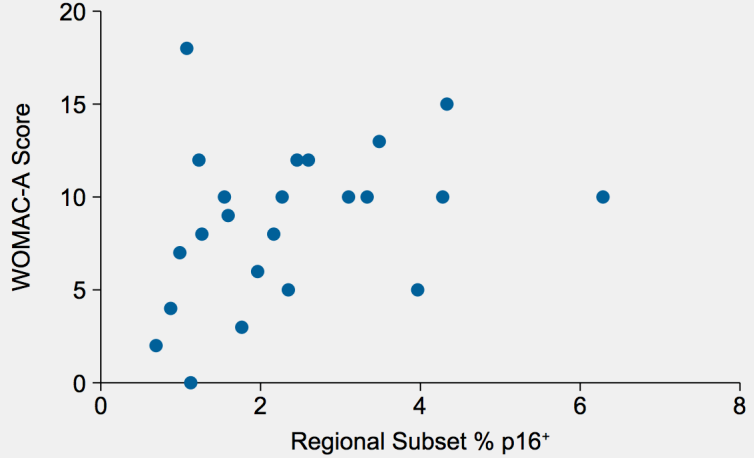
$p16^{INK4a+}$ IHC photomicrograph of a biopsy specimen
Red Arrow is synoviocyte/fibroblasts a few macrophages
Green Arrow is non senescent synoviocyte

Unity Biotechnology

OA Phase 0 Study Results

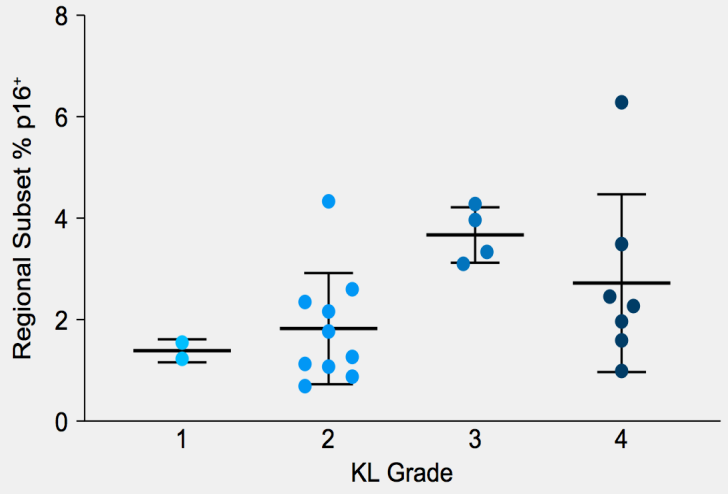
Correlation of Senescent Cell Burden with OA Disease Severity

Regional Subset p16 Correlation With WOMAC-A



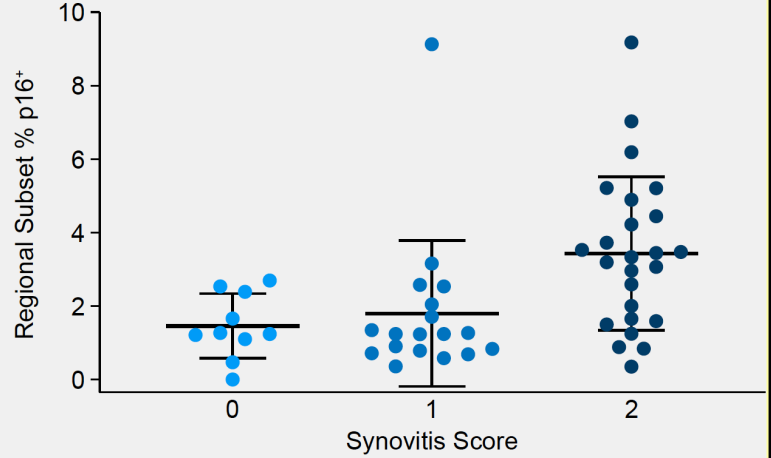
Partial Spearman's rank correlation: 0.471, p=0.042, n=23. Data adjusted for age and BMI. Regions 1, 2 and 3 analyzed.

Regional Subset p16 Correlation With KL



ANCOVA of % p16+. KL 1–4: p=0.156; 1–3: p=0.0317; 2–3: p=0.0305. Data adjusted for age and BMI. Regions 1, 2 and 3 analyzed. Mean ± standard deviation (SD) shown.

Regional Subset p16 Correlation With Synovitis



ANCOVA of % p16+. Synovitis 0–2: p=0.0298. Data adjusted for age and BMI. Regions 1, 2 and 3 analyzed. Mean ± SD shown.

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Yohn et al. [Abs 1982] *Arthritis Rheumatol* 2019;71(suppl 10).

UBX0101 Phase 1 Study Baseline Characteristics

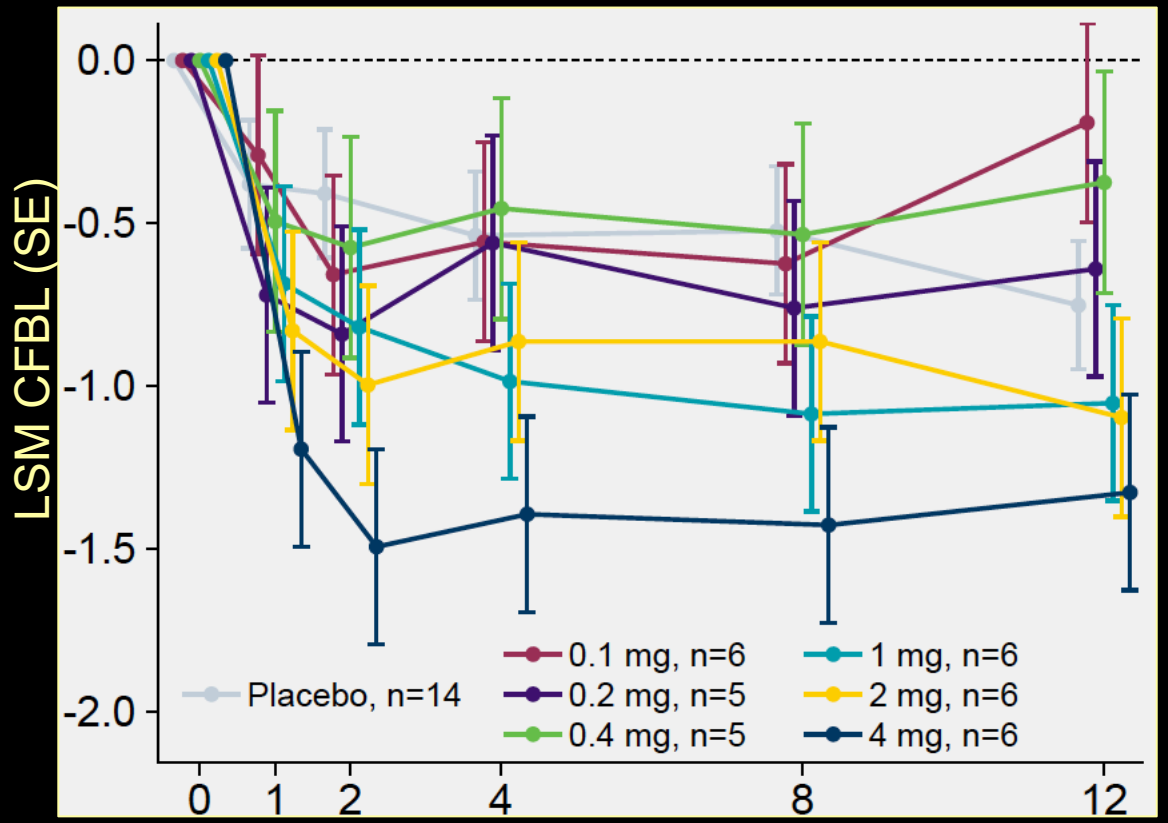
	Total N=48	Placebo n=14	UBX0101 n=34
KLG, n (%)			
1	5 (10.9)	2 (16.7)	3 (8.8)
2	6 (13.0)	2 (16.7)	4 (11.8)
3	29 (63.0)	7 (58.3)	22 (64.7)
4	6 (13.0)	1 (8.3)	5 (14.7)
Mean 11-pt synovitis score (SD)	12.30 (5.25)	13.36 (5.14)	11.85 (5.31)
Mean OA disease duration, y (SD)	11.30 (7.74)	10.74 (5.45)	11.53 (8.56)
Mean WOMAC item score (SD)			
A, pain	1.96 (0.46)	1.87 (0.44)	1.99 (0.47)
B, stiffness	2.29 (0.59)	2.47 (0.64)	2.22 (0.57)
C, function	1.97 (0.59)	1.93 (0.64)	1.99 (0.58)
Mean NRS weekly average (SD)	6.35 (1.16)	6.47 (1.11)	6.30 (1.20)

KLG, Kellgren-Lawrence grade; NRS, numeric rating scale; SD, standard deviation.

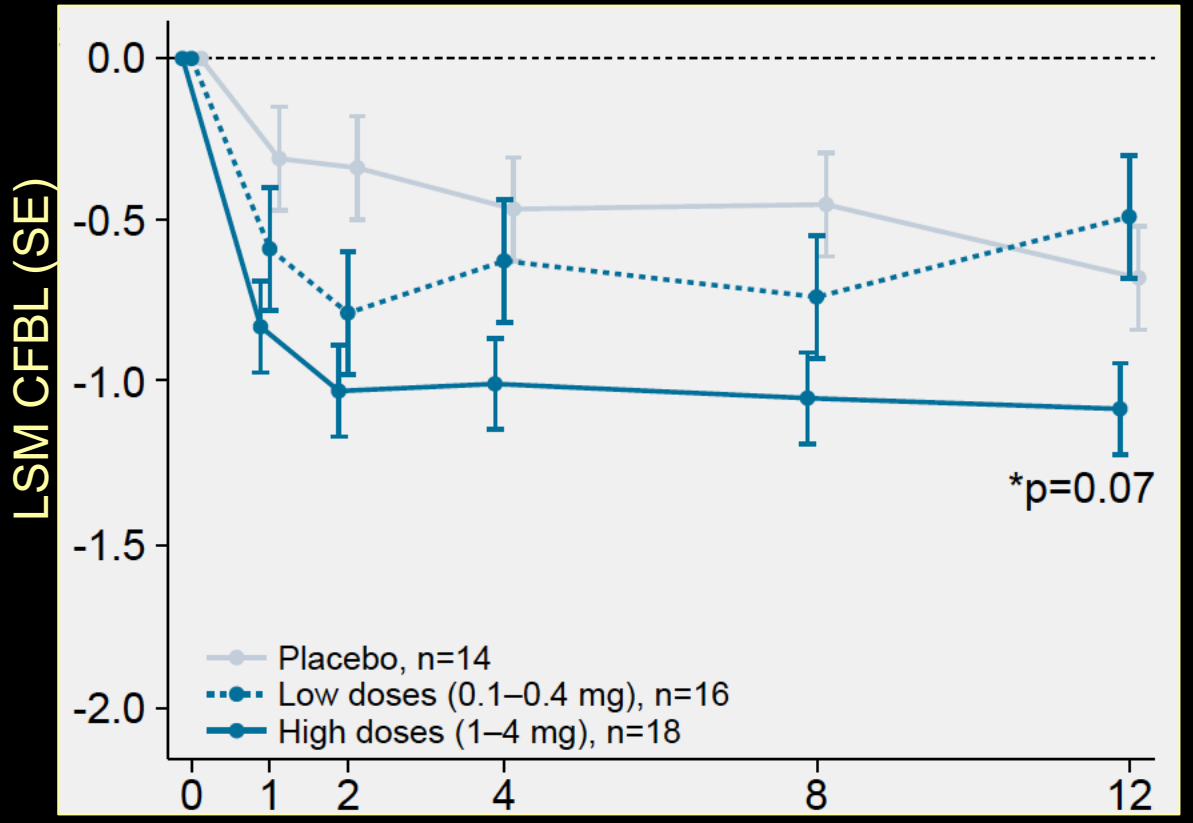
Hsu et al. [Abstract L05] *Arthritis Rheumatol* 2019;71 (suppl 10)

UBX0101 Phase 1 Study Efficacy Results

WOMAC-A – All Doses



WOMAC-A – Low and High Doses Groups



CFBL, change from baseline; LSM, least square mean; SE, standard error of the mean.

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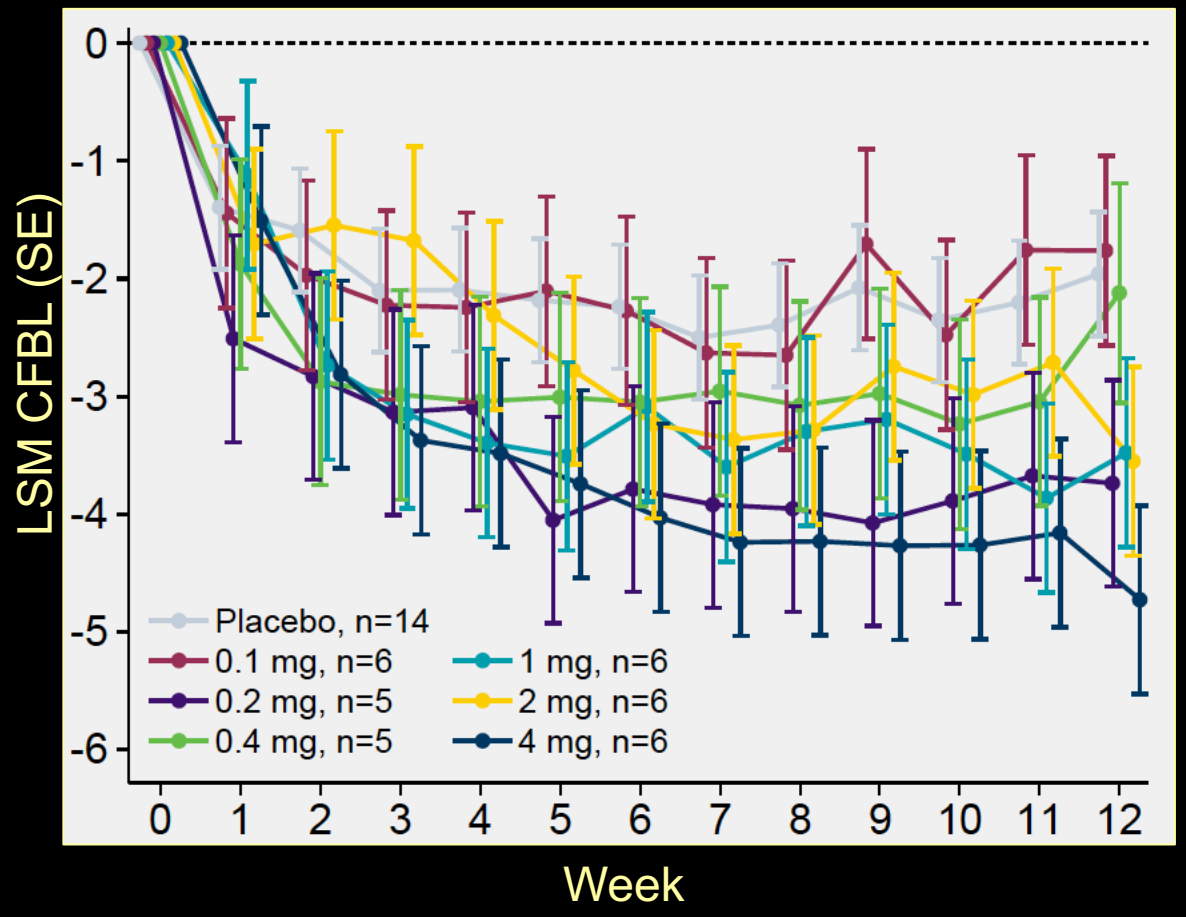
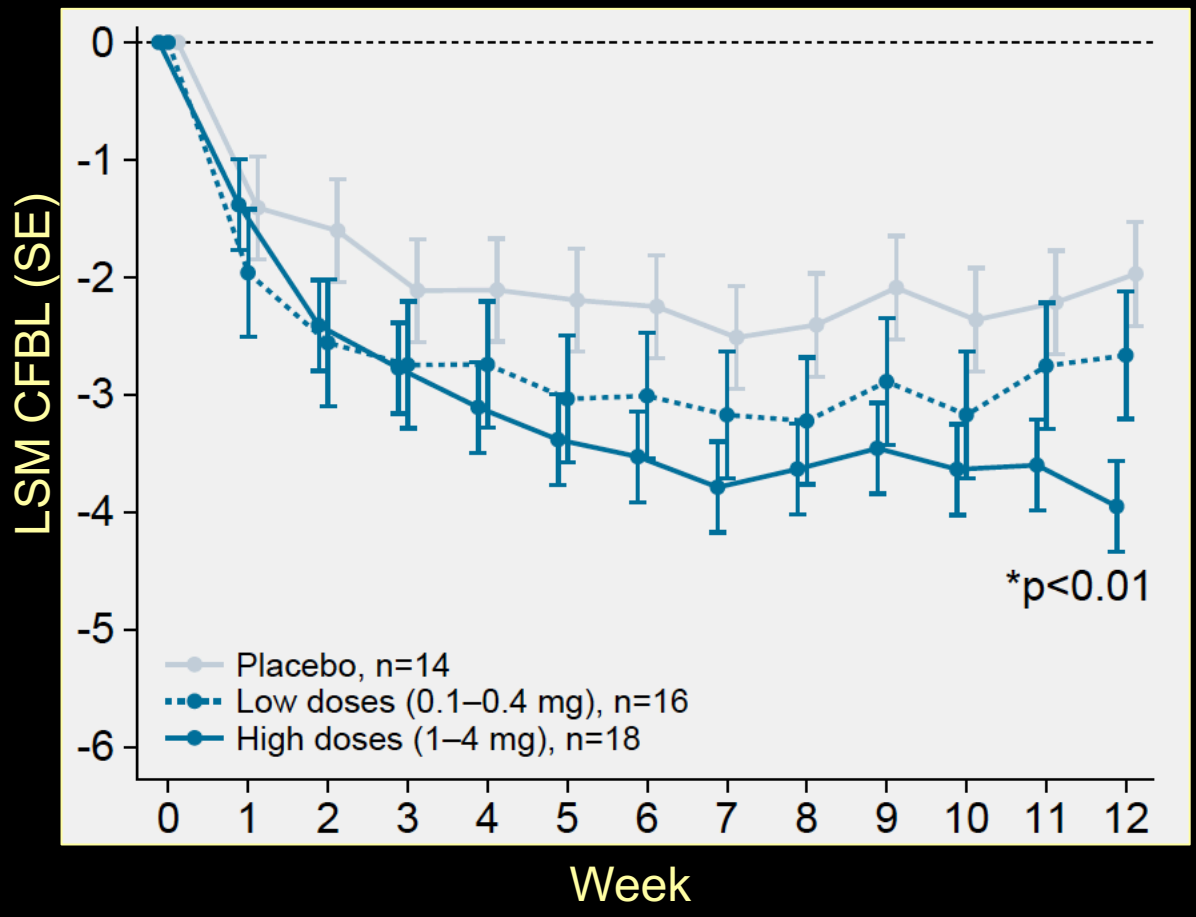
Hsu et al. [Abstract L05] *Arthritis Rheumatol* 2019;71 (suppl 10)

UBX0101 Phase 1 Study Efficacy Results

Pain NRS – All Doses



Pain NRS – Low and High Doses Groups



CFBL, change from baseline; LSM, least square mean; SE, standard error of the mean.

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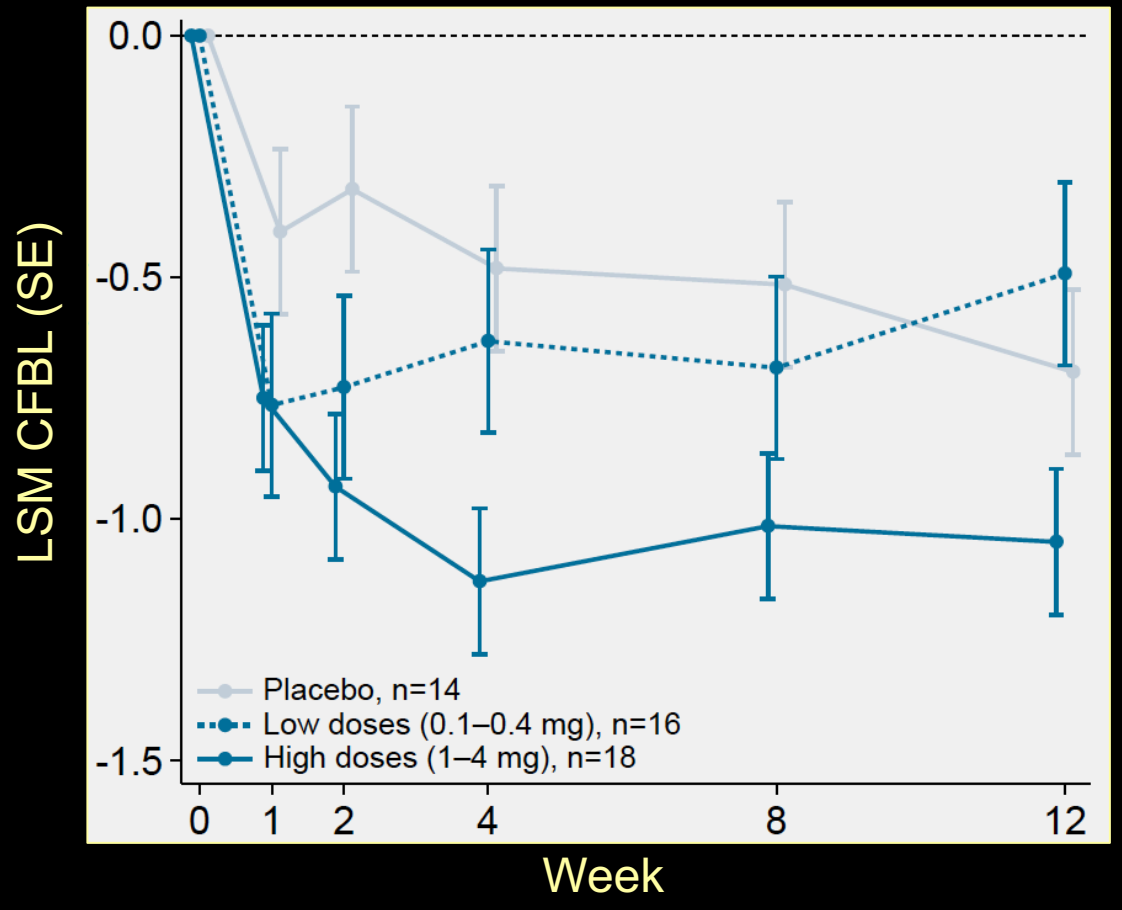
Hsu et al. [Abstract L05] *Arthritis Rheumatol* 2019;71 (suppl 10)

UBX0101 Phase 1 Study Efficacy Results

WOMAC-C – Low and High Doses Groups



CFBL, change from baseline; LSM, least square mean; SE, standard error of the mean.

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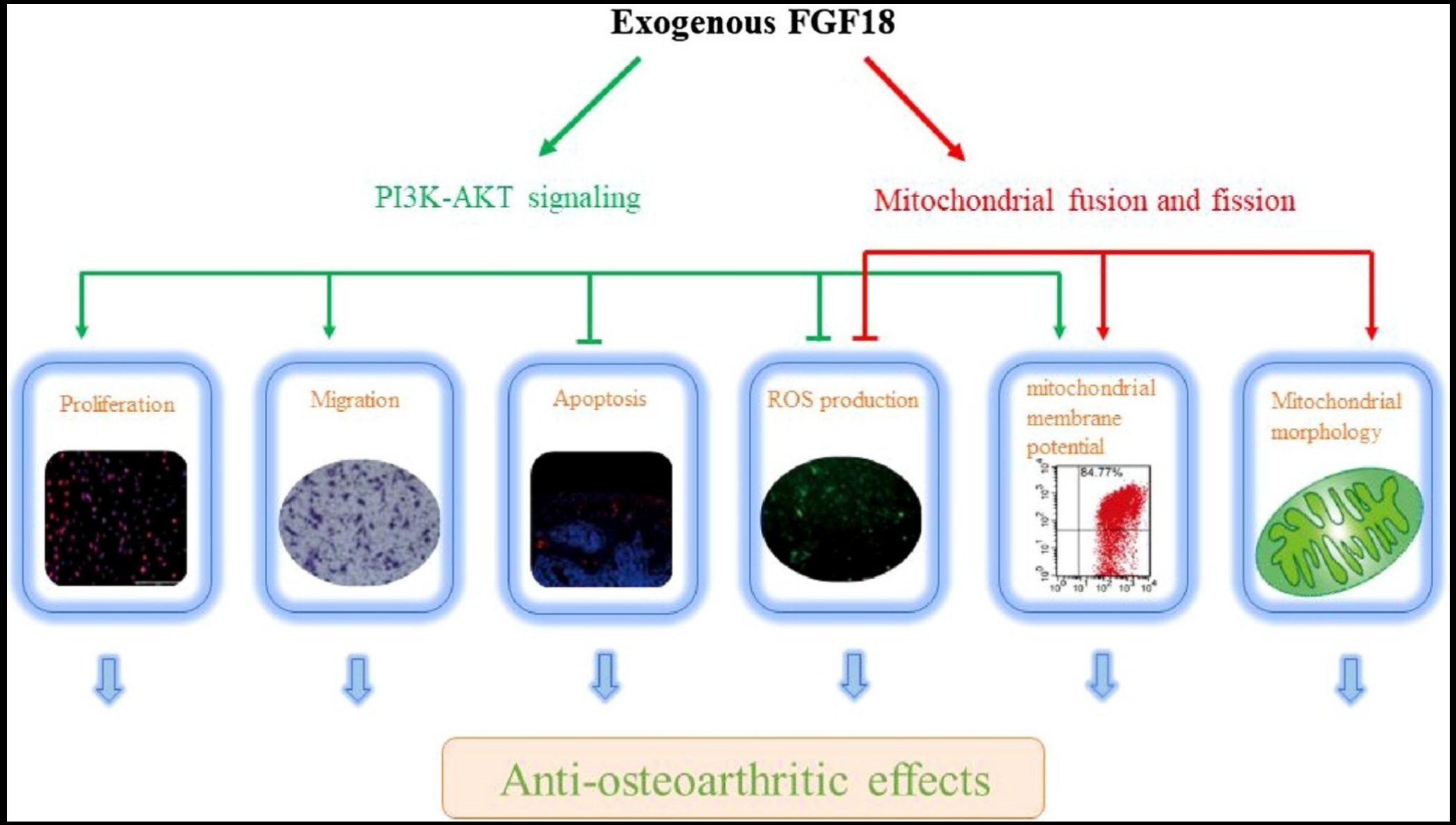
Hsu et al. [Abstract L05] *Arthritis Rheumatol* 2019;71 (suppl 10)

UBX0101 Phase 1 Study Summary

- This was an exploratory Phase 1 study in painful knee OA
- Single IA doses of UBX0101 up to 4 mg were well-tolerated by patients
- High doses of UBX0101 resulted in significant and clinically meaningful reductions of knee pain 12 weeks following treatment
- Modulation of SASP factors in the synovial fluid by UBX0101 treatment supports senolysis as a potential novel therapeutic mechanism in OA
- The safety and efficacy results of this study should be validated and extended in larger, adequately powered clinical trials

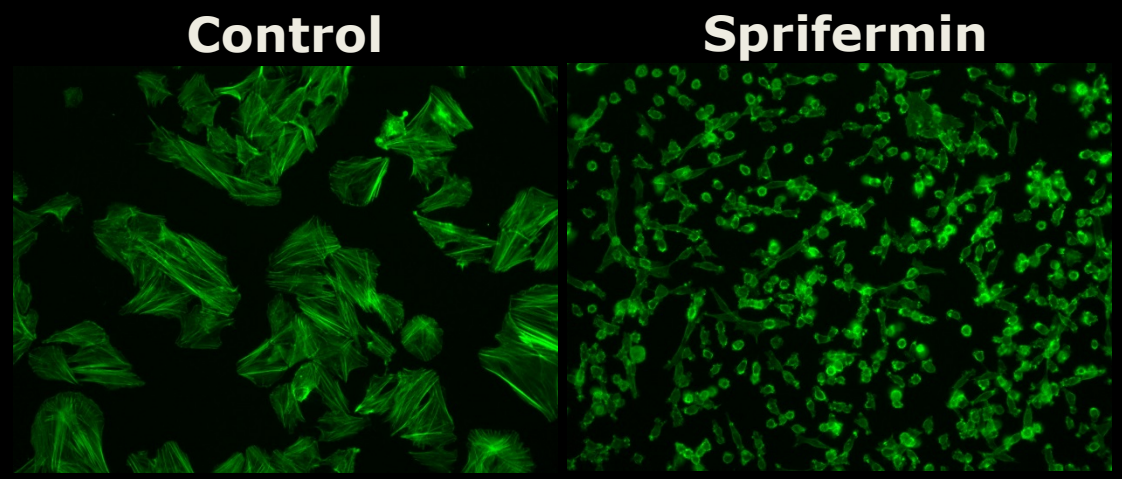
Hsu et al. [Abstract L05] *Arthritis Rheumatol* 2019;71 (suppl 10)

FGF18 for the treatment of knee OA through Intra-articular injections into the joint.

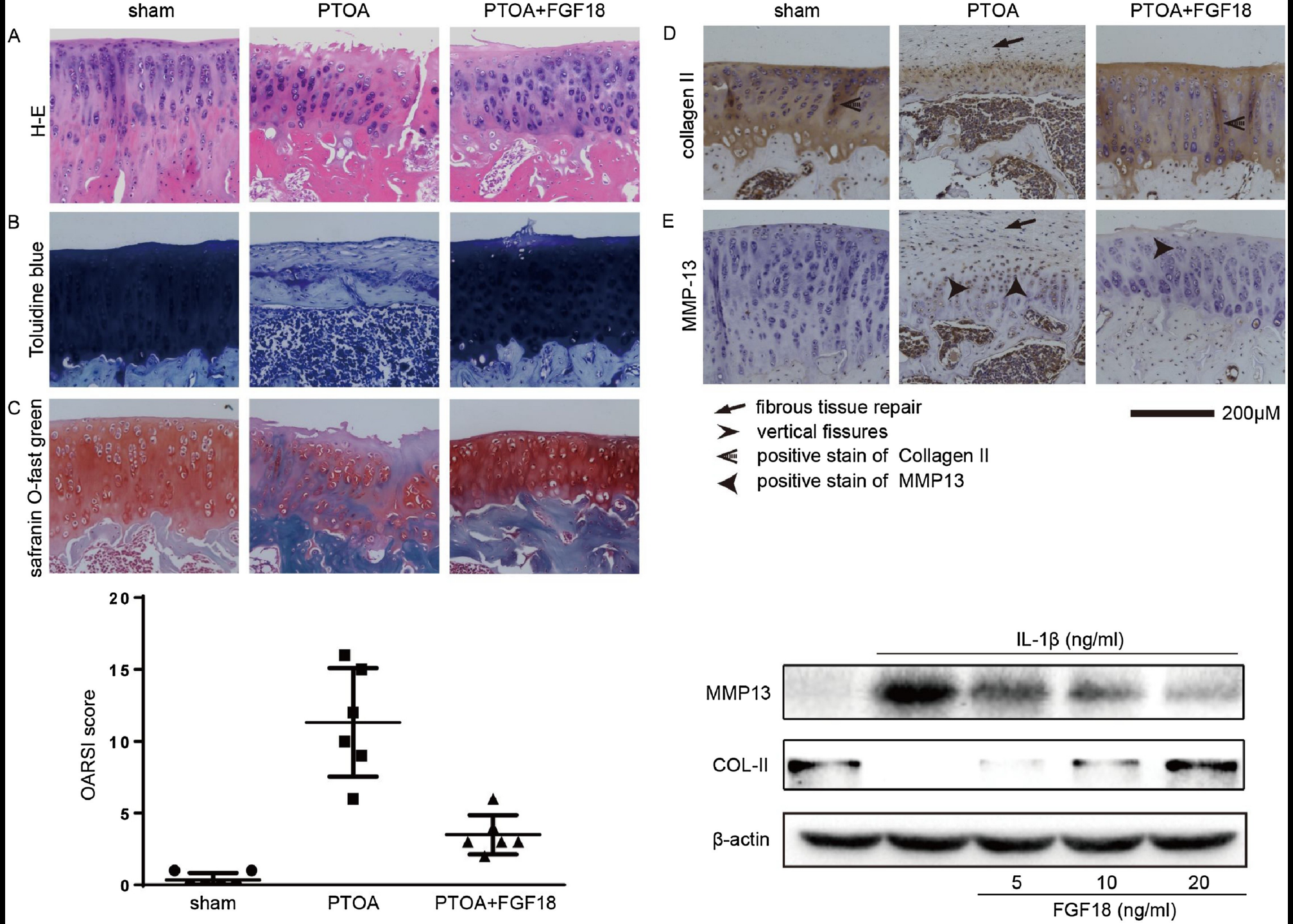

Exogenous FGF18
PI3K-AKT signaling
Mitochondrial fusion and fission
Proliferation
Migration
Apoptosis
ROS production
mitochondrial membrane potential
84.77%
Mitochondrial morphology
Anti-osteoarthritic effects

Recombinant human Fibroblast Growth Factor 18 (Sprifermin)

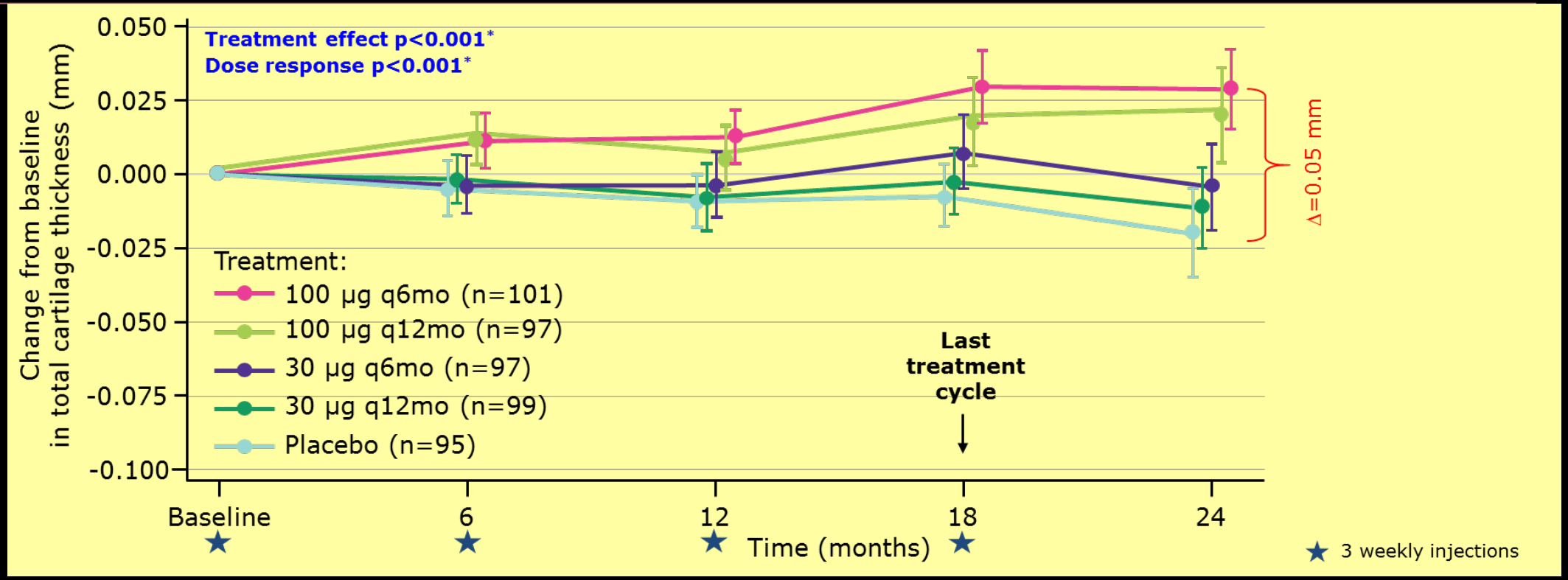
- Human version of naturally-occurring FGF-18
- Binds to FGF receptor 3 (FGFR3) on chondrocytes, leading to activation of intracellular signalling pathways and:
  - stimulation of chondrocyte proliferation
  - induction of anabolic phenotype
  - ECM production
  - Reduction of type I collagen expression



Porcine chondrocytes in monolayer culture, 7 days with 100 ng/mL of sprifermin
or in absence of compound (control)
The cell cytoskeleton (actin) was stained in green


sham
PTOA
PTOA+FGF18
A
H-E
B
Toluidine blue
C
safranin O-fast green
D
collagen II
E
MMP-13
fibrous tissue repair
vertical fissures
positive stain of Collagen II
positive stain of MMP13
200μM
OARSI score
20
15
10
5
0
sham
PTOA
PTOA+FGF18
IL-1β (ng/ml)
MMP13
COL-II
β-actin
5
10
20
FGF18 (ng/ml)

Sprifermin 5 yr Phase II trial: FORWARD

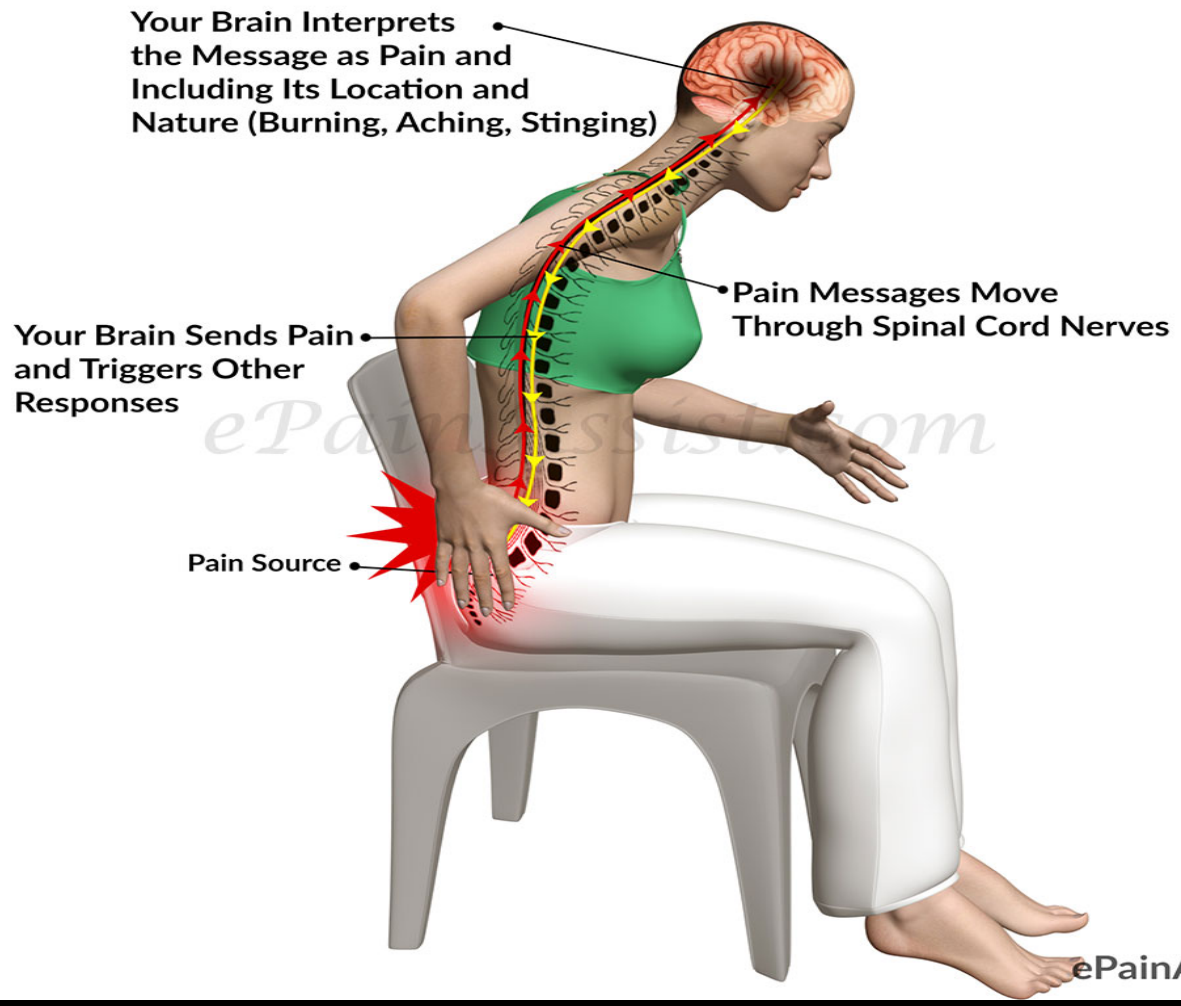


Primary endpoint met: dose-dependent increase in TFTJ cartilage thickness (qMRI), with significant differences for sprifermin 100 µg q6mo and 100 µg q12mo vs placebo

PAINWEEK

Hochberg MC et al. EULAR 2018

Chronic Nociceptive Pain



The appreciation of joint pain, will usually result in an individual reducing or Changing their activities to reduce the joint pain. PAIN response is protective

Neurotrophins: function in the mature PNS and CNS and modulate Nociceptive Pain

Neurotrophin	Receptors
Nerve growth factor (NGF)	p75, TrkA
Brain-derived neurotrophic factor (BDNF)	p75, TrkB
Neurotrophin 3 (NT-3)	p75, TrkC
Neurotrophin 4 (NT-4)	p75, TrkB

Nerve Growth Factor (NGF) Discovery

- Rita Levi-Montalcini (Italy) and Stanley Cohen at University of Washington, St. Louis - recipients of the Nobel Prize in 1986

- Isolated NGF in the 1950s through observations of certain cancerous tissues could cause extremely rapid growth of nerve cells
- Determined that NGF was critical for survival of small, mainly unmyelinated peripheral sensory neurons and sympathetic post ganglionic neurons during development
- Affect on adult nociceptive neurons less well characterized and not appreciated until years later

Acad Sci USA. 1960;46:301–311
Levi-Montalcini R et al. Proc Natl Acad Sci USA. 1960;46(3):373–384.
Levi-Montalcini R et al. Proc Natl Acad Sci USA. 1960;46(3):384–391

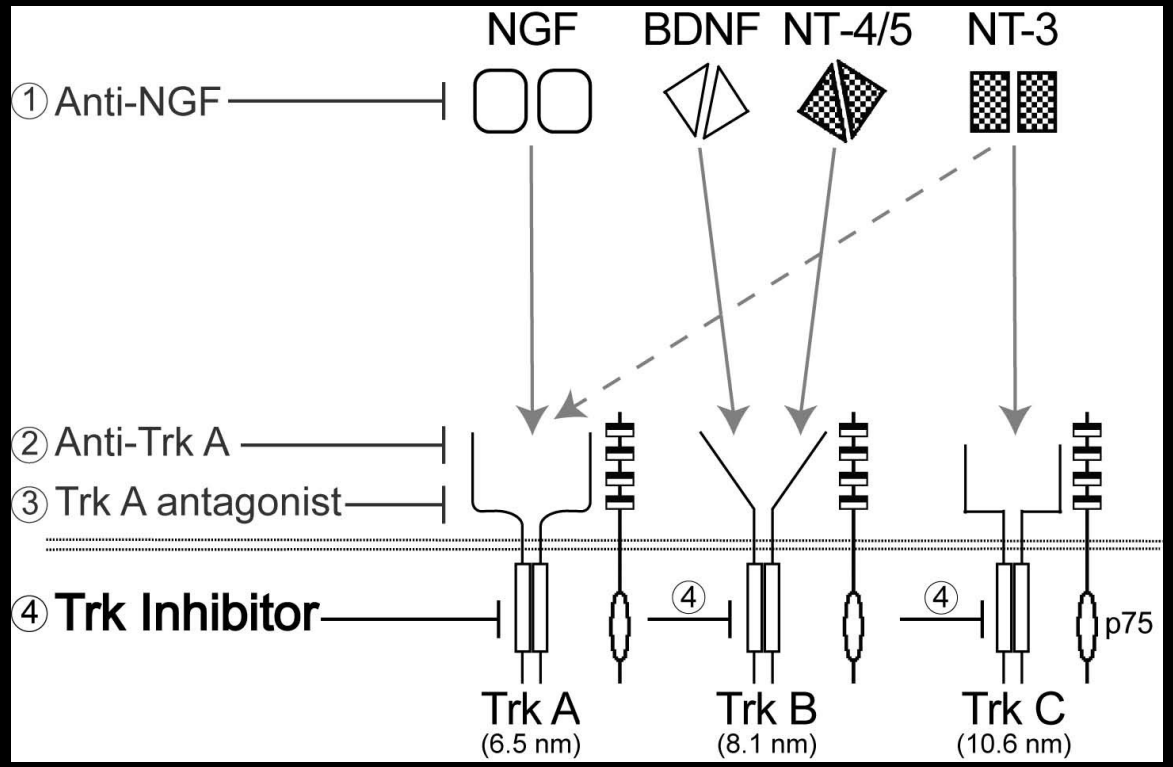
Nerve Growth Factor (NGF)

Ribbon Cartoon of Mature Human NGF

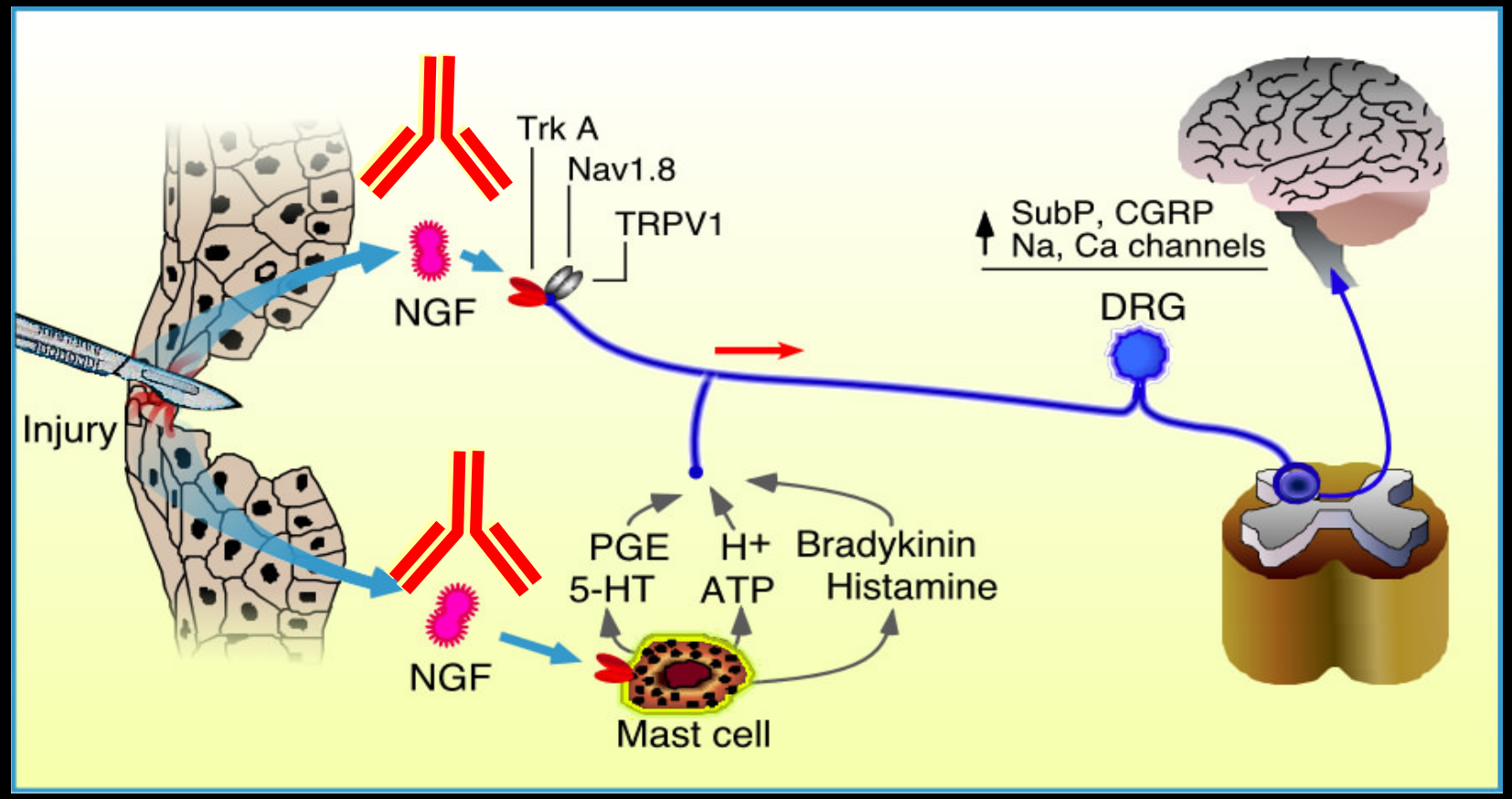
- NGF is a protein produced by different cell types, such as muscle cells, epithelial cells, fibroblasts, adipocytes, neurons, glia, and immune cells[1]
  - Induced by proinflammatory cytokines released by damaged tissue in the periphery
- NGF is also synthesized in the brain[2]
- NGF is a homodimer consisting of two strands each 120 amino acids, which non-covalently dimerize to form a 26 kDa protein[3]

1. Minnone et al. J Mol Sci. 2017;18(5)
2. Persson. Seminars in The Neurosciences. 1994;(5):227-237
3. Allen and Dawbarn. Clinical Science.2006;110:175–191

NGF and Trk A receptor are located on nociceptive neurons in peripheral nervous system



NGF-mediated pain pathways



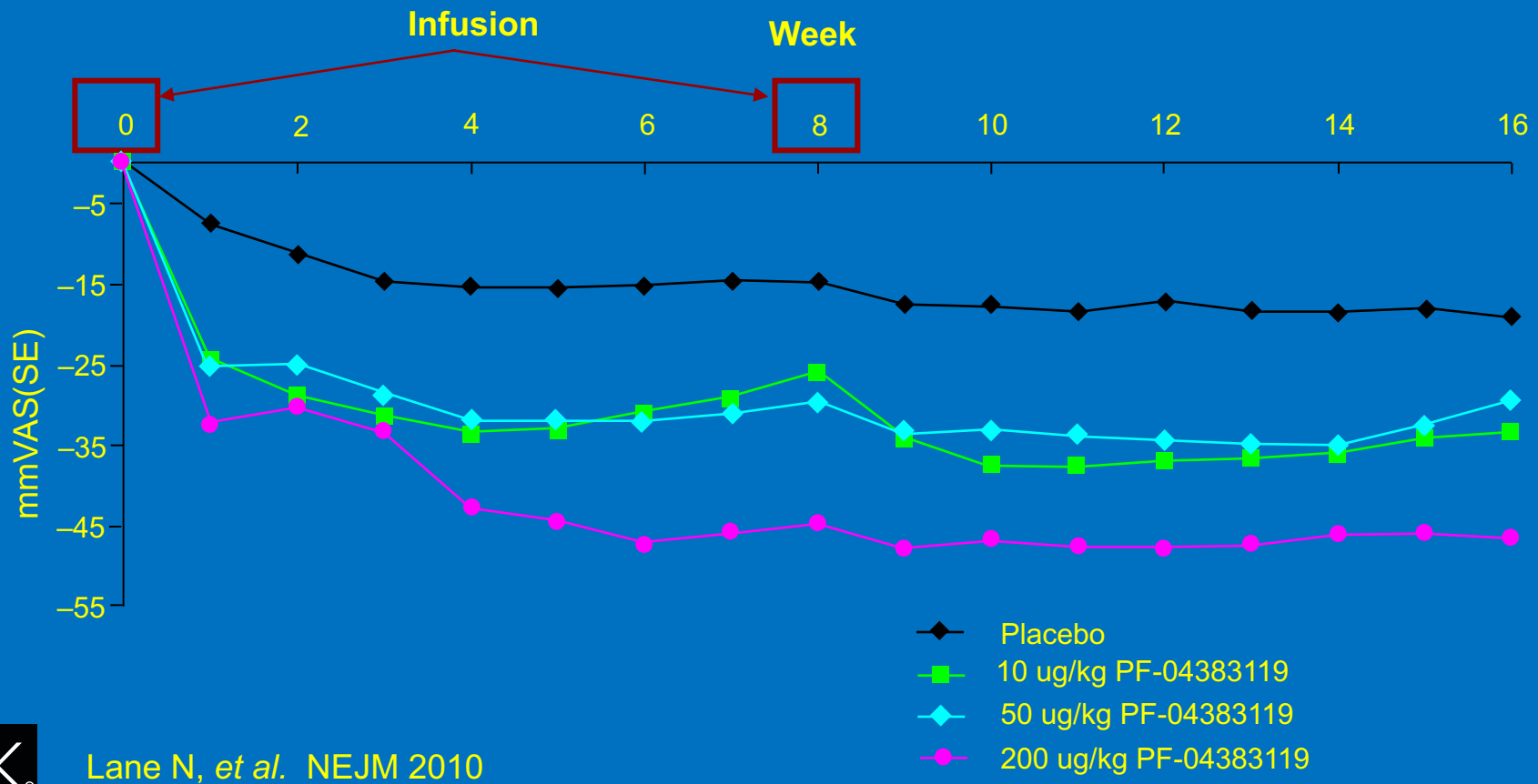
- NGF modulates pain signalling pathways, so there significant interest in analgesic potential of NGF inhibition

Baseline characteristics

	Placebo	Tanezumab (μg/kg)				
		10	25	50	100	200
	N = 74	N = 74	N = 74	N = 74	N = 74	N = 74
Age, yr (SD)	58.1 (7.7)	58.3 (8.3)	59.9 (8.1)	60.4 (7.7)	57.1 (8.2)	58.4 (7.6)
Female, %	56.8	66.2	67.6	50.0	59.5	54.1
K/L grade 3- 4, %*	74.0	70.3	68.0	61.1	70.3	72.2
Walking knee pain, VAS mm	71.6	70.6	71.7	68.1	71.1	72.4
SGA, VAS mm	48.8	55.7	51.0	51.6	49.9	54.4
WOMAC pain, VAS mm (	69.0	65.8	69.2	62.1	68.3	68.4

LANE N Engl J Med. 2010 Oct 14;363(16):1521-31

Tanezumab : Walking Pain in Index Knee
Mean Change from Baseline



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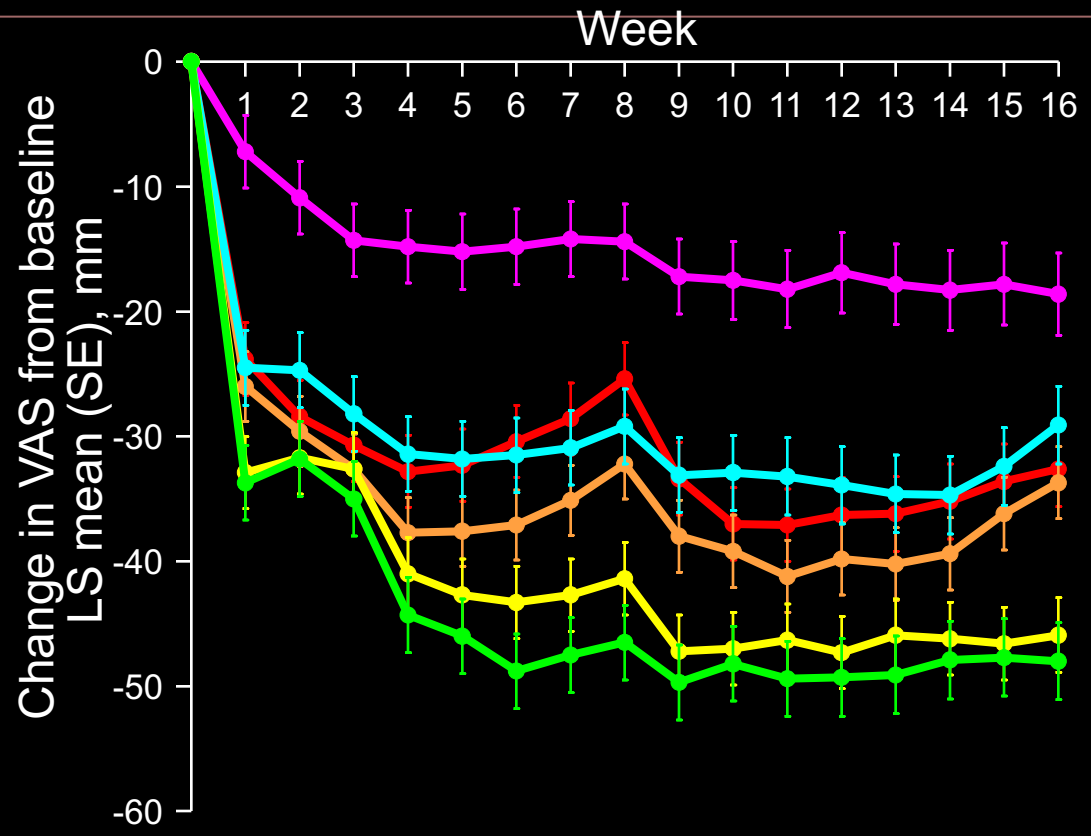
Lane N, *et al.* NEJM 2010

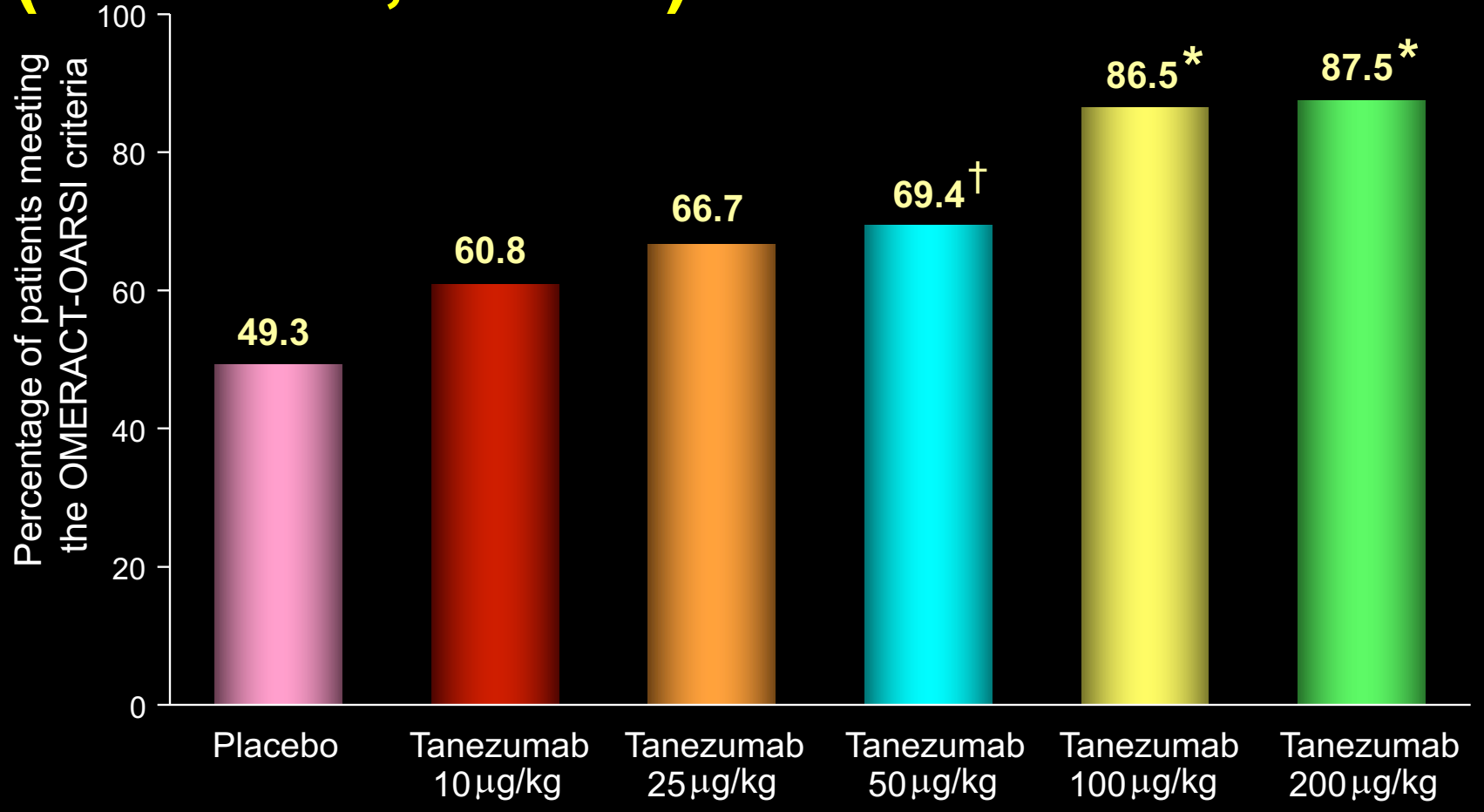
Walking knee pain
(Mean change ± standard error)



	Mean change from baseline over Weeks 1-16 (SE)
Placebo	-15.5 (2.6)
Tanezumab 10μg/kg	-32.1 (2.5)*
Tanezumab 25μg/kg	-36.0 (2.5)*
Tanezumab 50μg/kg	-31.0 (2.6)*
Tanezumab 100μg/kg	-42.5 (2.5)*
Tanezumab 200μg/kg	-45.2 (2.6)*

*P<0.001 vs placebo

OMERACT-OARSI responder analysis (Week 16, LOCF)



†P<.05, *P<.001 vs placebo

PainWeek

Lane et al NEJM 2010

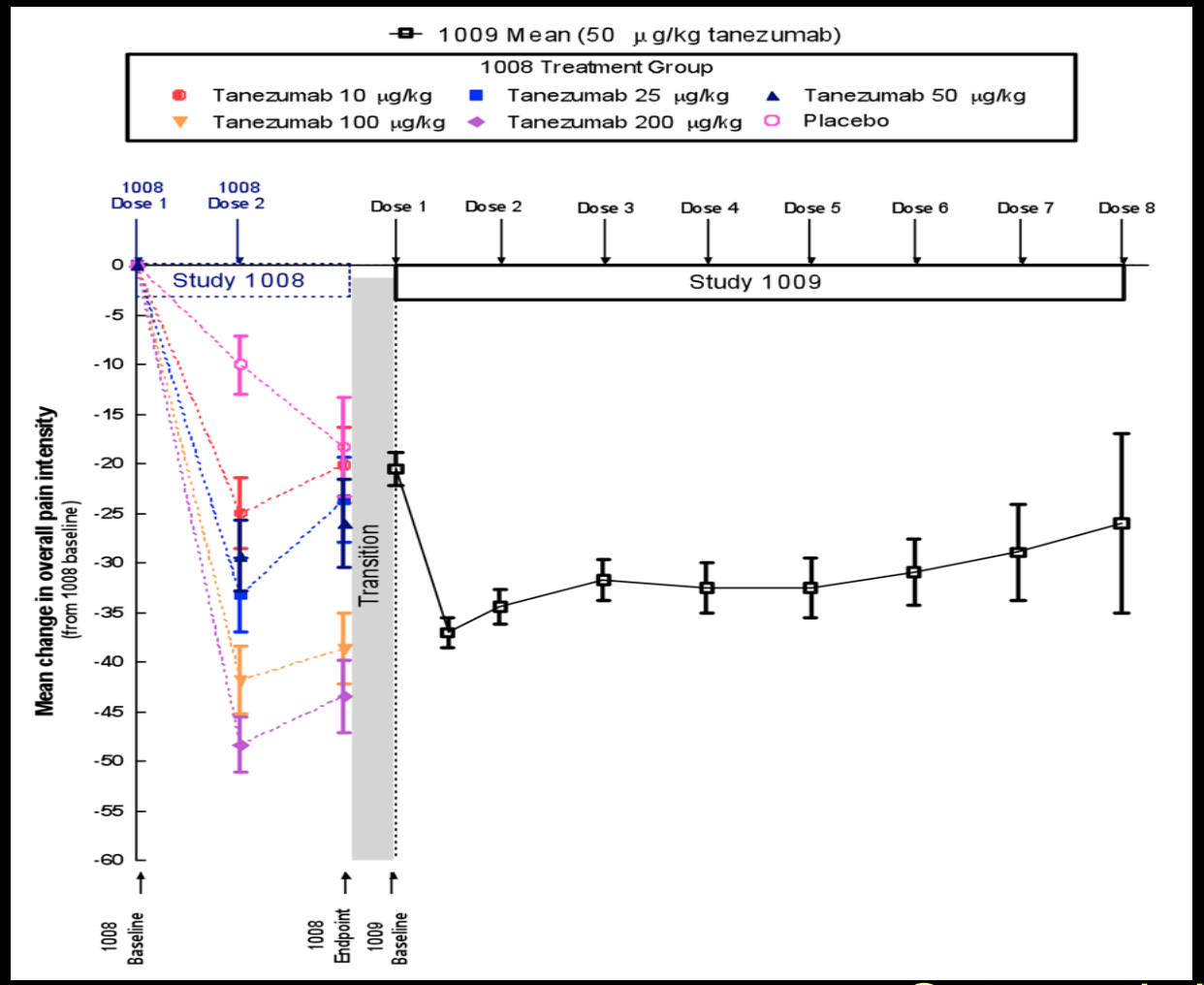
Safety Assessments

% of patients	Placebo N = 74	Tanezumab (μg/kg) 10 N = 74	25 N = 74	50 N = 74	100 N = 74	200 N = 74
Any AE	55.4	68.9	66.2	59.5	68.9	78.4
Treatment-related AE	8.1	14.9	17.6	10.8	28.4	35.1
Any serious AE	1.4	2.7	0	2.7	0	2.7
Discontinued due to AE	0	8.1	1.4	5.4	4.1	10.8
AEs of abnormal peripheral sensation						
Paresthesia	2.7	5.4	5.4	1.4	10.8	10.8
Hyperesthesia	0	0	0	4.1	5.4	5.4
Allodynia	0	0	0	0	1.4	1.4
Dysesthesia	0	0	0	0	1.4	1.4

PainWeek

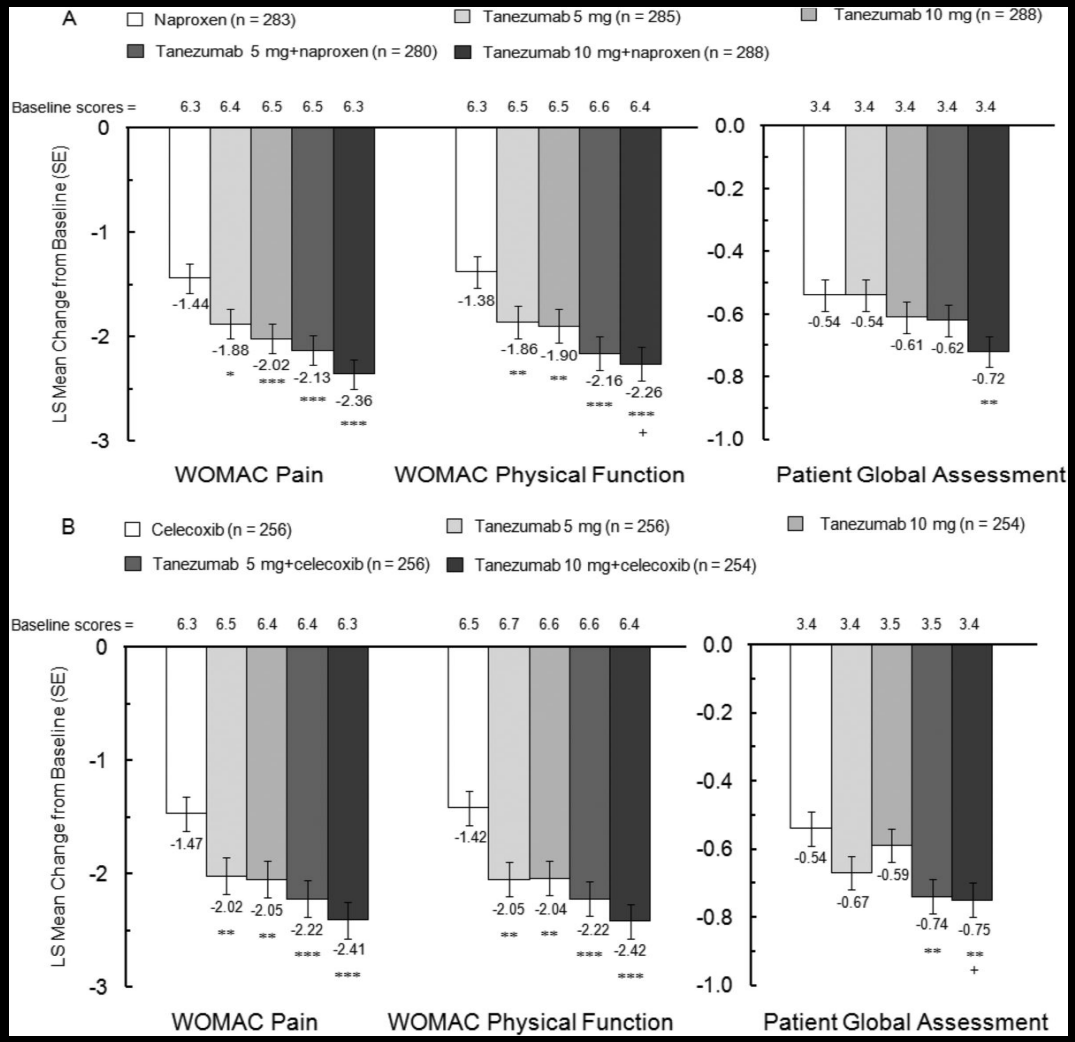
Lane NEJM, 2010

Tanezumab 1009 Study Results.



Lane NE, Schnitzer T, et al, Osteoarthritis Cartilage . 2011 Jun;19(6):639-46.

Phase Iii Studies of Change from baseline to week 16 in the WOMAC Pain subscale, WOMAC Physical Function subscale and Patient's Global Assessment of OA



Schnitzer T J et al. Ann Rheum Dis
doi:10.1136/annrheumdis-2013-204905

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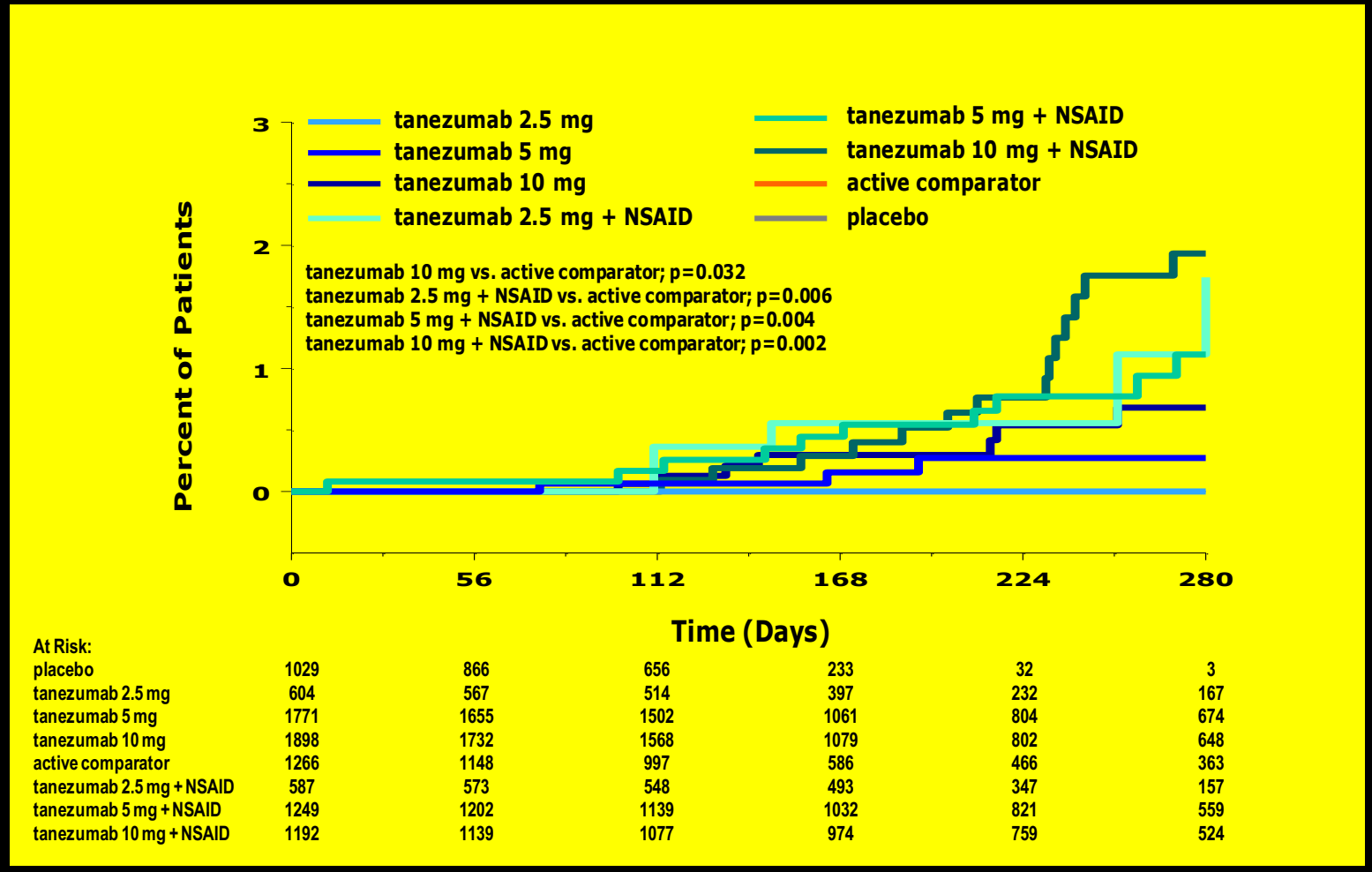
ARD

Time to Rapidly Progression hip and knee OA



At Risk:						
placebo	1029	866	656	233	32	3
tanezumab 2.5 mg	604	567	514	397	232	167
tanezumab 5 mg	1771	1655	1502	1061	804	674
tanezumab 10 mg	1898	1732	1568	1079	802	648
active comparator	1266	1148	997	586	466	363
tanezumab 2.5 mg + NSAID	587	573	548	493	347	157
tanezumab 5 mg + NSAID	1249	1202	1139	1032	821	559
tanezumab 10 mg + NSAID	1192	1139	1077	974	759	524

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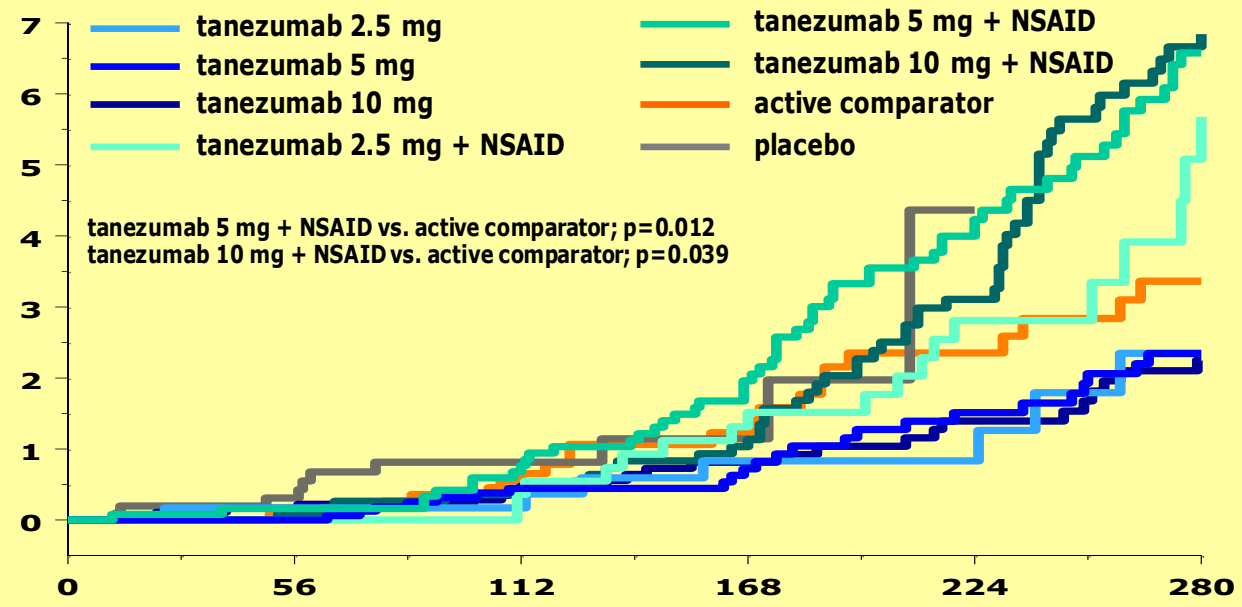
Hochberg MC, Tive LA, Abramson SB, Vignon E, Verburg KM, West CR, Smith MD, Hungerford DS.Arthritis Rheumatol. 2016 Feb;68(2):382-91

Time to Total Joint Replacement by TZB Dose and Regimen



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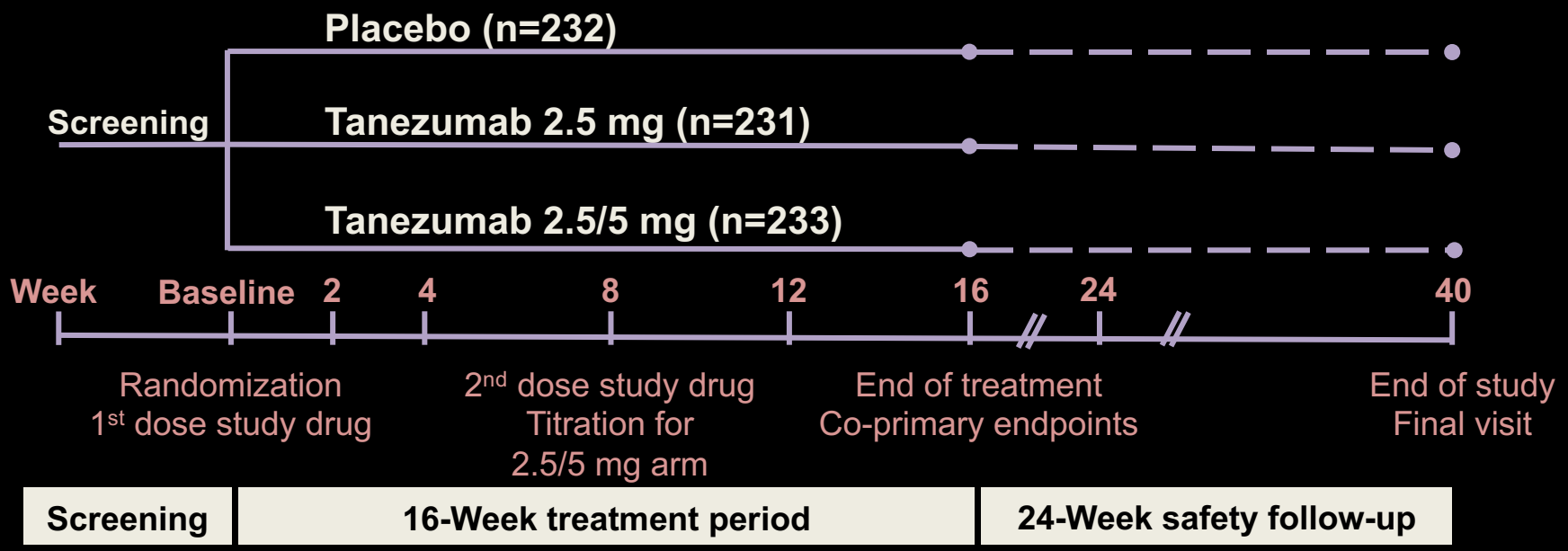
tanezumab 10 mg + NSAID	1192	1139	1077	974	759	524

Hochberg et al, Osteoarthritis and Cartilage 2015

Background, Objective and Study Design

Study Objective: To assess the efficacy and safety of subcutaneous (SC) tanezumab 2.5 mg and 2.5 mg titrated to 5 mg at Week 8 vs placebo in patients with moderate to severe OA

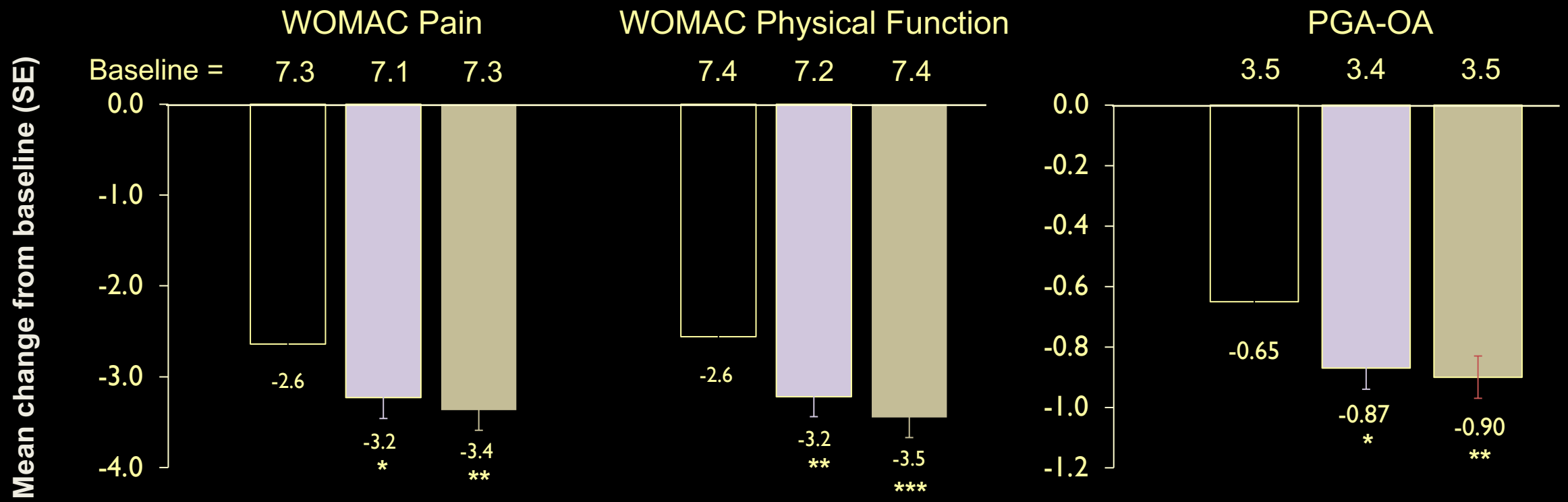
Study Design:



1. Mantyh PW, et al. *Anesthesiology* 2011;115:189-204. **2.** Schnitzer TJ, Marks JA. *Osteoarthritis Cartilage* 2015;23(Suppl 1):S8-17.

Co-Primary Efficacy Endpoints

Both tanezumab treatment groups met co-primary endpoints for study



* $P \leq 0.05$; ** $P \leq 0.01$; *** $P \leq 0.001$ vs placebo.

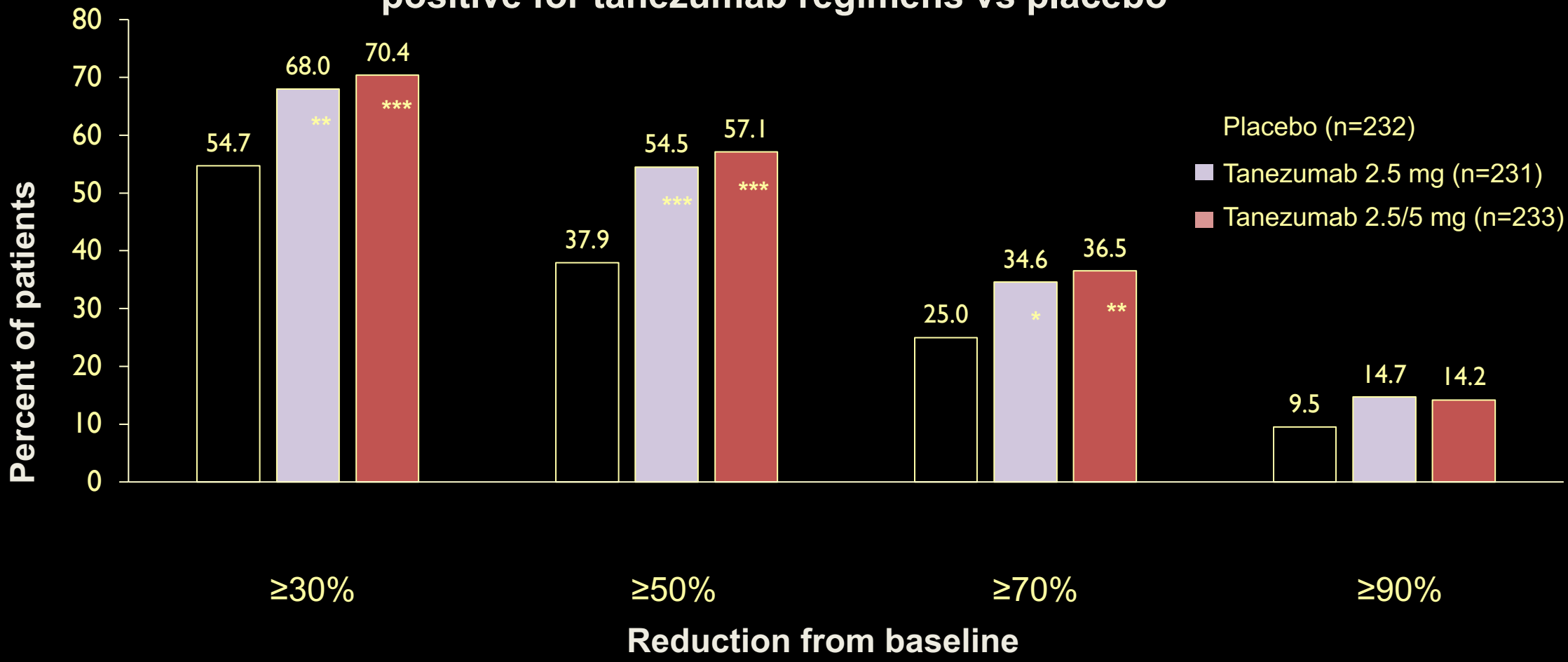
Placebo (n=232) Tanezumab 2.5 mg (n=231) Tanezumab 2.5/5 mg (n=233)

PainWeek

T. Schnitzer, Richard Easton, MD,[2] Shirley Pang, MD,[3] Dennis J. Levinson, MD,[4]Glenn Pixto
MS,[5] Lars Viktrup, MD, PhD,[6] Isabelle Davignon, PhD,[7] Mark T. Brown, MD,[7]Christine R. Wes
PhD [7] and Kenneth M. Verburg, PhD[7] JAMA. 2019 Jul 2; 322(1): 37–48

WOMAC Pain Responder Rates at Week 16

Key secondary endpoint ≥50% reduction in WOMAC Pain—positive for tanezumab regimens vs placebo



▪T. Schnitzer, Richard Easton, MD, Shirley Pang, MD,Dennis J. Levinson, MD,[4]Glenn Pixton, MS,[5] Lars Viktrup, MD, PhD,[6] Isabelle Davignon, PhD,[7] Mark T. Brown, MD,[7]Christine R. West, PhD,[7] and Kenneth M. Verburg, PhD[7]JAMA. 2019 Jul 2; 322(1): 37–48.

Summary of Joint Safety Events

Number (%) of patients	Placebo (n=232)	Tanezumab 2.5 mg (n=231)	Tanezumab 2.5/5 mg (n=233)
Adjudicated joint safety events	5 (2.2)	14 (6.1)	18 (7.7)
Normal progression of OA	5 (2.2)	8 (3.5)	17 (7.3)
Rapidly progressive OA type 1	0	3 (1.3)	1 (0.4)
Rapidly progressive OA type 2	0	2 (0.9)	0
Other (pre-existing SIF)	0	1 (0.4)	0
Total joint replacements (TJRs)	4 (1.7)	8 (3.5)	16 (6.9)
Knee	4	3	9[a]
Hip	0	5	7

- Incidence of rapidly progressive OA ([RPOA] type 1 + type 2; 6/464, 1.3%) in combined tanezumab group aligned with expectations based on the risk mitigation procedures used
- The cause of the treatment imbalance in TJRs in this study is unknown, but it is inconsistent with prior tanezumab studies

Schnitzer TJ, JAMA 2019 Jul 2; 322(1): 37–48

[a]

SIF = subchondral insufficiency fracture

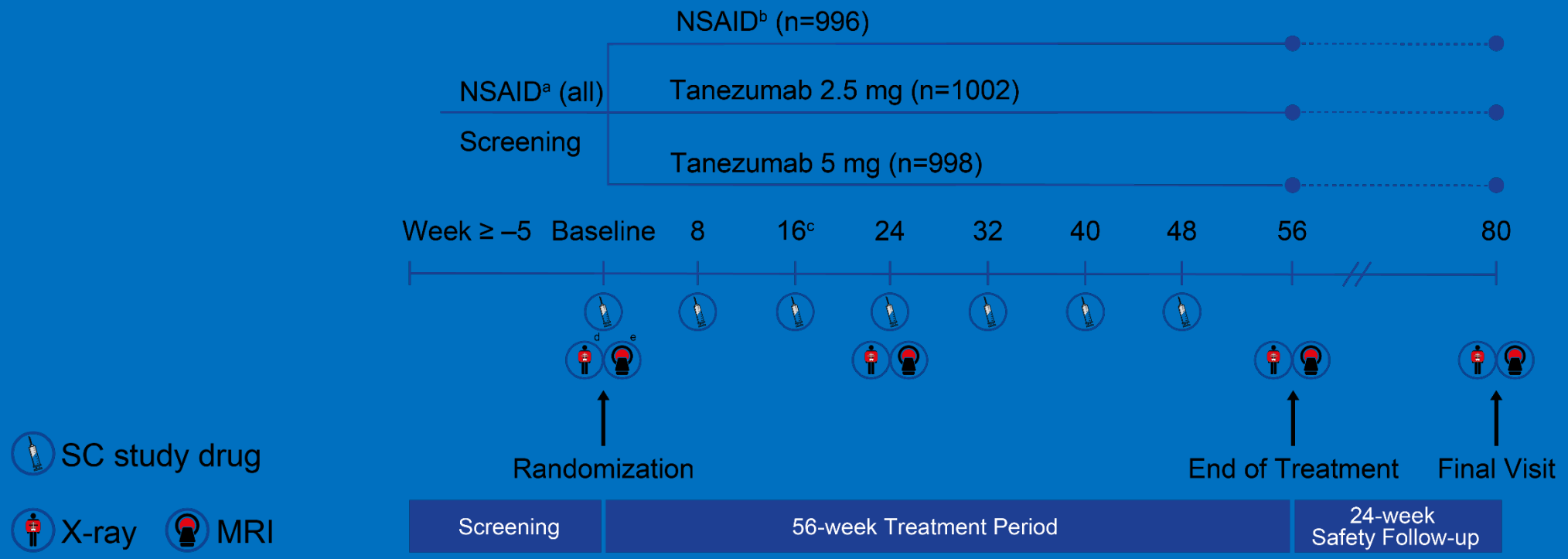
Subcutaneous Tanezumab Versus NSAID for the Treatment of Osteoarthritis: Joint Safety Events in a Randomized, Double-Blind, Active-Controlled, 80-Week, Phase-3 Study

- Hochberg[1], John A Carrino[2], Thomas J Schnitzer[3], Ali Guermazi[4], David A Walsh[5], Alexander White[6], Satoru Nakajo[7], Robert Fountaine[8], Anne Hickman[8], Glenn Pixton[9],
  Lars Viktrup[10], Mark T Brown[8], Christine R West[8], Kenneth M Verburg[8]
- *[1]University of Maryland School of Medicine, Baltimore, MD, USA; [2]Hospital for Special Surgery, New York, NY USA; [3]Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [4]Boston University School of Medicine, Boston,*
  MA, USA, [5]University of Nottingham School of Medicine, Nottingham, UK; [6]Progressive Medical Research, Port Orange, FL, USA; [7]Nakajo Orthopaedic Clinic, Japan; [8]Pfizer Inc, Groton, CT, USA; [9]Pfizer Inc, Morrisville, NC; [10]Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, USA

American AMer oAMerican f Rheumatology/Association of Rheumatology Health Professionals (ACR/ARHP) Annual Meeting, November 8–13, 2019, Atlanta, GA, USA

Study Design

- A phase 3, randomized, double-blind, double-dummy, NSAID-controlled, parallel-group study conducted at 446 centers in 18 countries



Joint Safety Endpoints

- Primary composite joint safety endpoint
  - Rapidly progressive OA type 1a or type 2b (RPOA1 or RPOA2), primary osteonecrosis, subchondral insufficiency fracture, or pathologic fracture (combined, Week 0–80)
- Other joint safety endpoints
  - RPOA1, RPOA2, primary osteonecrosis, subchondral insufficiency fracture, and pathologic fracture (individually, Week 0–80)
  - Total joint replacement (TJR; Week 0–80)

[a] Defined as a significant loss of joint space width ≥2 mm (predicated on optimal joint positioning) within approximately 1 year, without gross structural failure.[1]
[b] Defined as abnormal bone loss or destruction, including limited or total collapse of at least 1 subchondral surface, which is not normally present in conventional end-stage OA.[1]

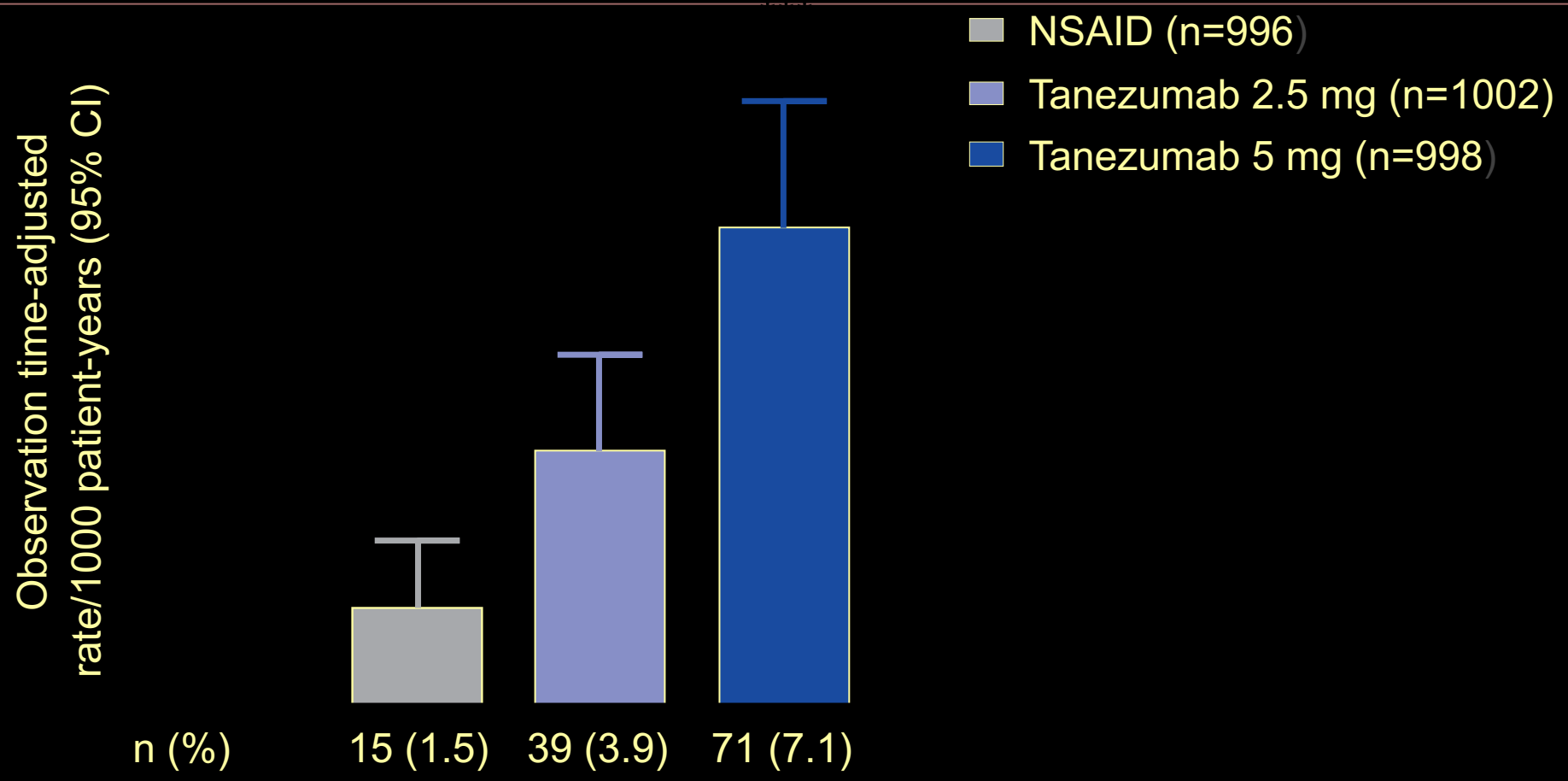
1. Miller CG, et al. *Osteoarthritis Cartilage* 2015;23:S3-S7.

Patient Demographics and Baseline Clinical Characteristics

Characteristic	NSAID (n=996)	Tanezumab 2.5 mg (n=1002)	Tanezumab 5 mg (n=998)
Female, n (%)	662 (66.5)	637 (63.6)	654 (65.5)
Age, years, mean (SD)	60.3 (9.5)	60.3 (9.2)	61.2 (9.6)
Race, n (%)			
White	680 (68.3)	705 (70.4)	712 (71.3)
Black	186 (18.7)	166 (16.6)	162 (16.2)
Other	130 (13.1)	131 (13.1)	124 (12.4)
Index joint, n (%)			
Hip	144 (14.5)	151 (15.1)	148 (14.8)
Knee	852 (85.5)	851 (84.9)	850 (85.2)
KLG[a] of index joint, n (%)			
0–1	4 (0.4)	2 (0.2)	6 (0.6)
2	291 (29.2)	298 (29.7)	303 (30.4)
3	476 (47.8)	475 (47.4)	474 (47.5)
4	225 (22.6)	227 (22.7)	215 (21.5)
WOMAC Pain subscale[b] score, mean (SD)	7.0 (1.1)	7.0 (1.1)	7.0 (1.1)
WOMAC Physical Function subscale[b] score, mean (SD)	7.0 (1.1)	7.1 (1.1)	7.1 (1.1)
PGA-OA[c] score, mean (SD)	3.4 (0.6)	3.5 (0.6)	3.5 (0.6)

[a] KLG for OA severity classification: 0 (no OA) to 4 (severe OA). [b] WOMAC Pain and Physical Function subscale scores: 11-pt numeric rating scales, 0–10 (higher scores = greater pain intensity and worse physical function, respectively). [c] PGA-OA scores: 5-point Likert scale (1 = “very good” to 5 = “very poor”). SD, standard deviation

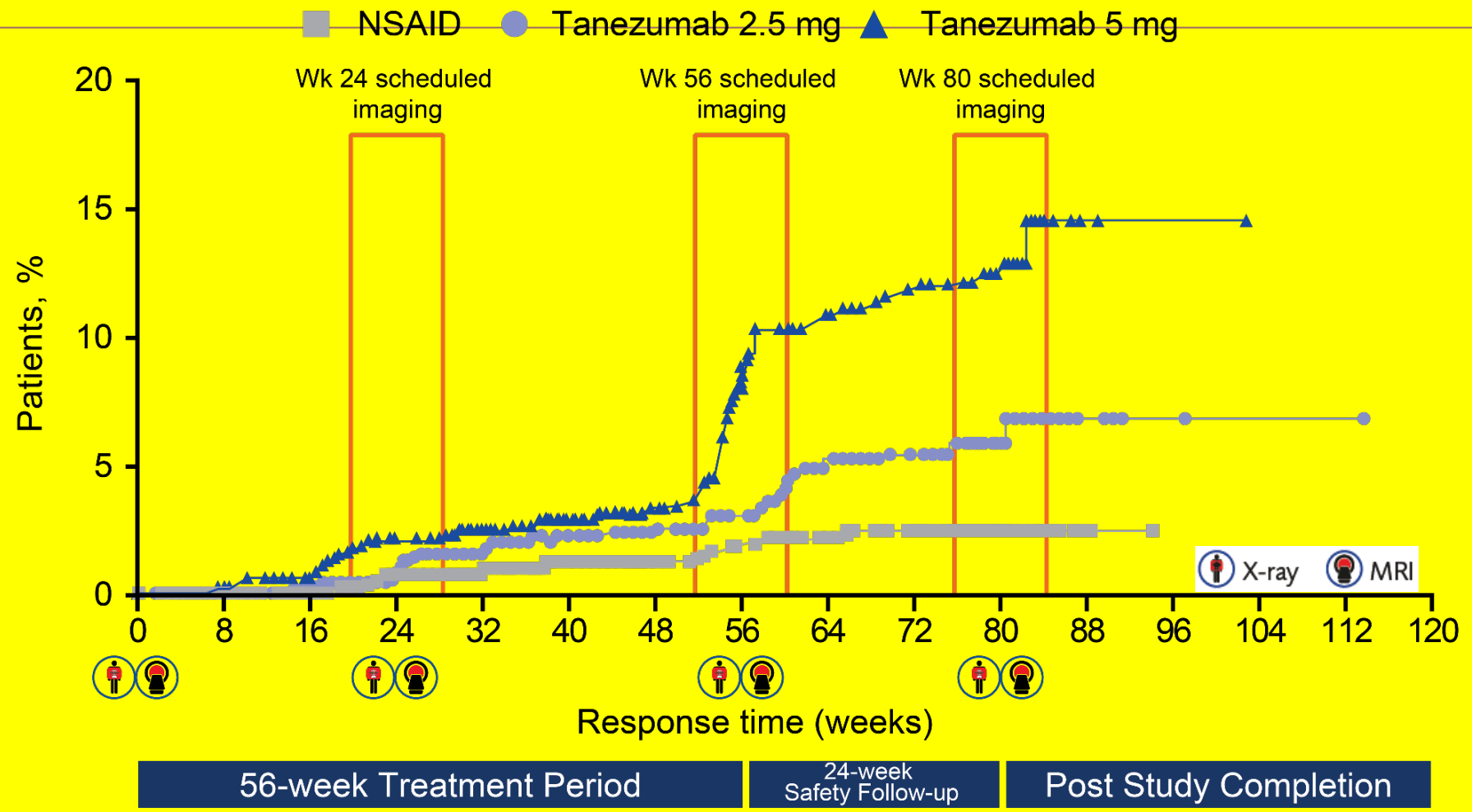
Primary Composite Joint Safety Endpoint



*$P \leq 0.05$; ** $P \leq 0.01$; *** $P \leq 0.001$ vs. NSAID

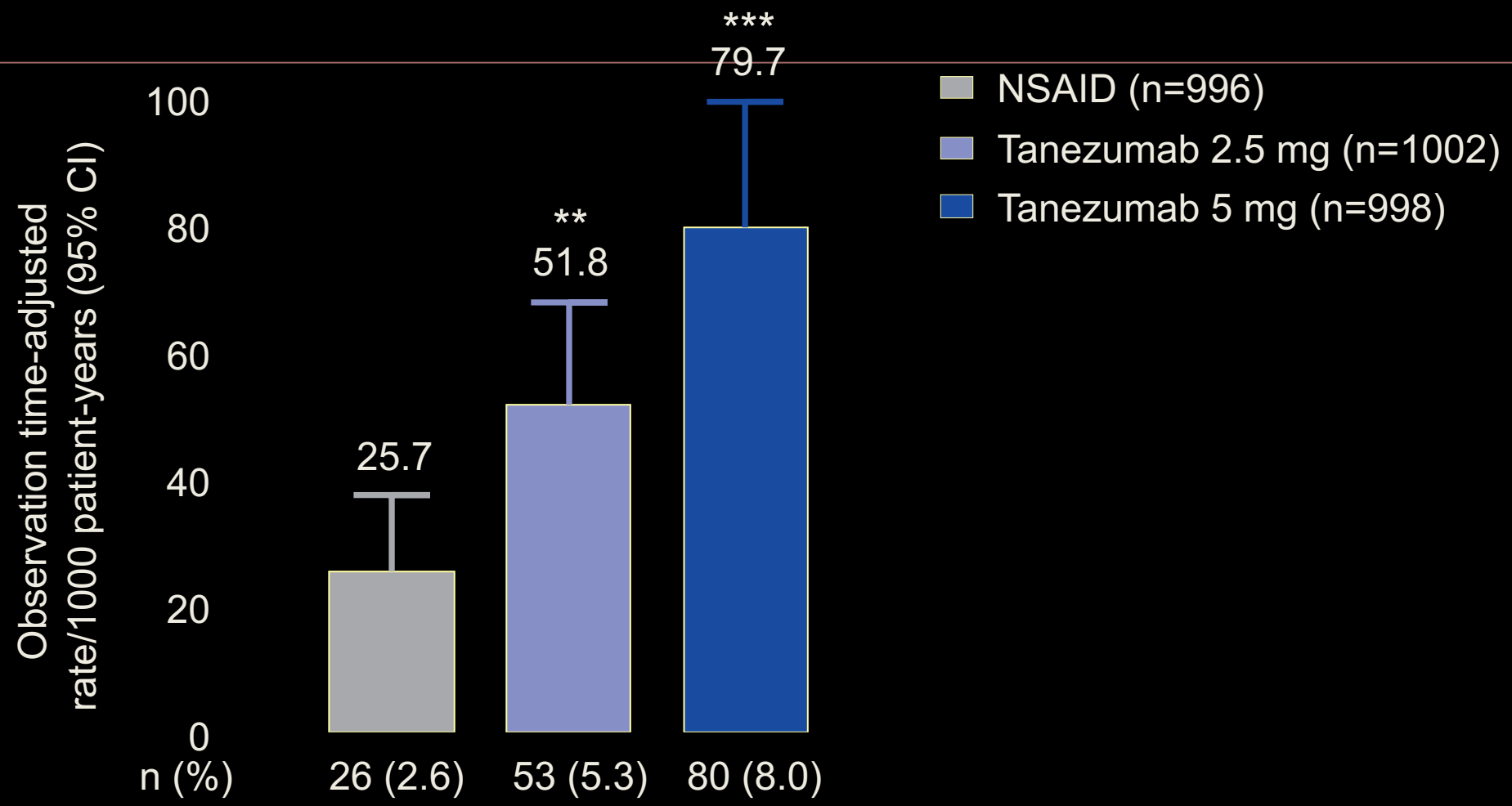
Primary composite joint safety endpoint: RPOA1 or RPOA2, primary osteonecrosis, subchondral insufficiency fracture, or pathologic fracture.

Time to the Primary Composite Joint Safety Endpoint



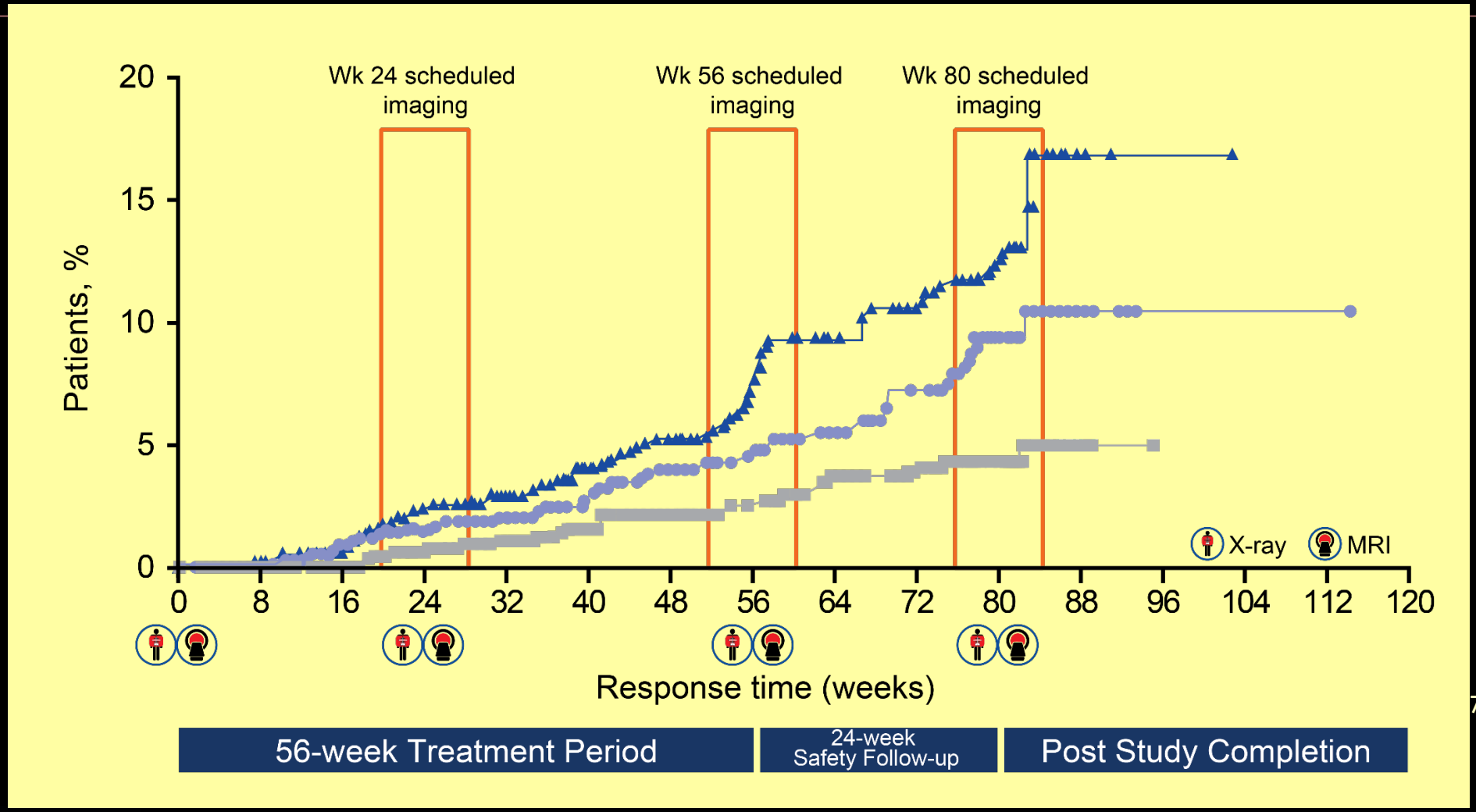
Intent-to-treat population; observed data; Kaplan–Meier estimates of time to event.

TJRs



*$P \leq 0.05$; ** $P \leq 0.01$; *** $P \leq 0.001$ vs. NSAID

Time to Total Joint Replacement



Adjudicated Joint Safety Endpoints in Patients With TJRs

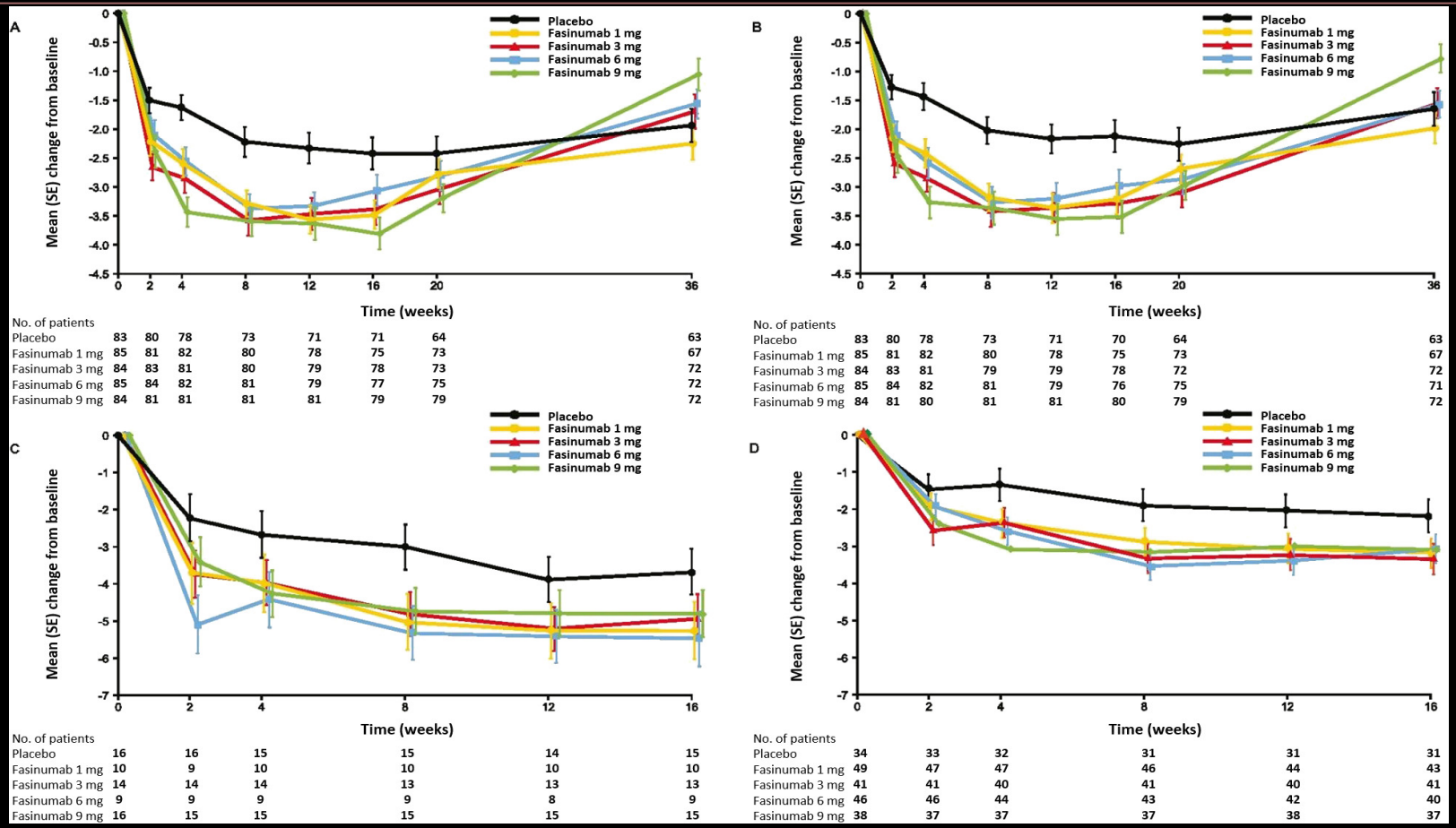
	No. of patients (%)		
	NSAID (n=996)	Tanezumab 2.5 mg (n=1002)	Tanezumab 5 mg (n=998)
TJR	26 (2.6)	53 (5.3)	80 (8.0)
TJR and adjudicated primary composite joint safety endpoint[a]	4 (0.4)	4 (0.4)	20 (2.0)
RPOA1	2 (0.2)	3 (0.3)	7 (0.7)
RPOA2	1 (0.1)	1 (0.1)	9 (0.9)
Primary osteonecrosis	0	0	1 (0.1)
Subchondral insufficiency fracture	1 (0.1)	0	3 (0.3)

Conclusions

- In this population of patients with OA and moderate-to-severe pain and functional disability despite prior stable doses of NSAIDs, tanezumab SC was associated with significantly more joint safety events than NSAIDs in a dose-dependent fashion.
- Tanezumab 5 mg SC had the least favorable joint safety profile.
- Tanezumab 2.5 mg SC had a more favorable joint safety profile than tanezumab 5 mg.
- The incidence of TJRs was significantly higher in the tanezumab 2.5-mg group than NSAIDs.

The Efficacy, Tolerability, and Joint Safety of Fasinumab in Osteoarthritis Pain: A Phase IIb/III Double-Blind, Placebo-Controlled, Randomized Clinical Trial

Controlled, Randomized Clinical Trial



Dakin P, et al Arthritis Rheumatol .2019 Nov;71(11):1824-1834

PAINWEEK

Adjudicated arthropathies and total joint replacements

	Placebo (n = 82)	Fasinumab				
		1 mg (n = 85)	3 mg (n = 84)	6 mg (n = 85)	9 mg (n = 83)	Combined (n = 337)
Arthropathies[b]						
No. of arthropathies	1	2	4	6	12	24
Patients with ≥1 arthropathy	1 (1.2)	2 (2.4)	4 (4.8)	6 (7.1)	10 (12.0)	22 (6.5)
RPOA[c]	0	2 (2.4)	2 (2.4)	5 (5.9)	7 (8.4)	16 (4.7)
Subchondral insufficiency fracture	1 (1.2)	0	2 (2.4)	1 (1.2)	3 (3.6)	6 (1.8)
Joint replacements						
No. of joint replacements	4	3	4	4	3	14
Patients with ≥1 joint replacement[d]	3 (3.7)	3 (3.5)	3 (3.6)	4 (4.7)	3 (3.6)	13 (3.9)
No. of joint replacements per 1,000 patient-years[e]	81.2	56.5	73.8	72.7	53.8	64.2

Dakin et al et al Arthritis Rheumatol .2019 Nov;71(11):1824-1834

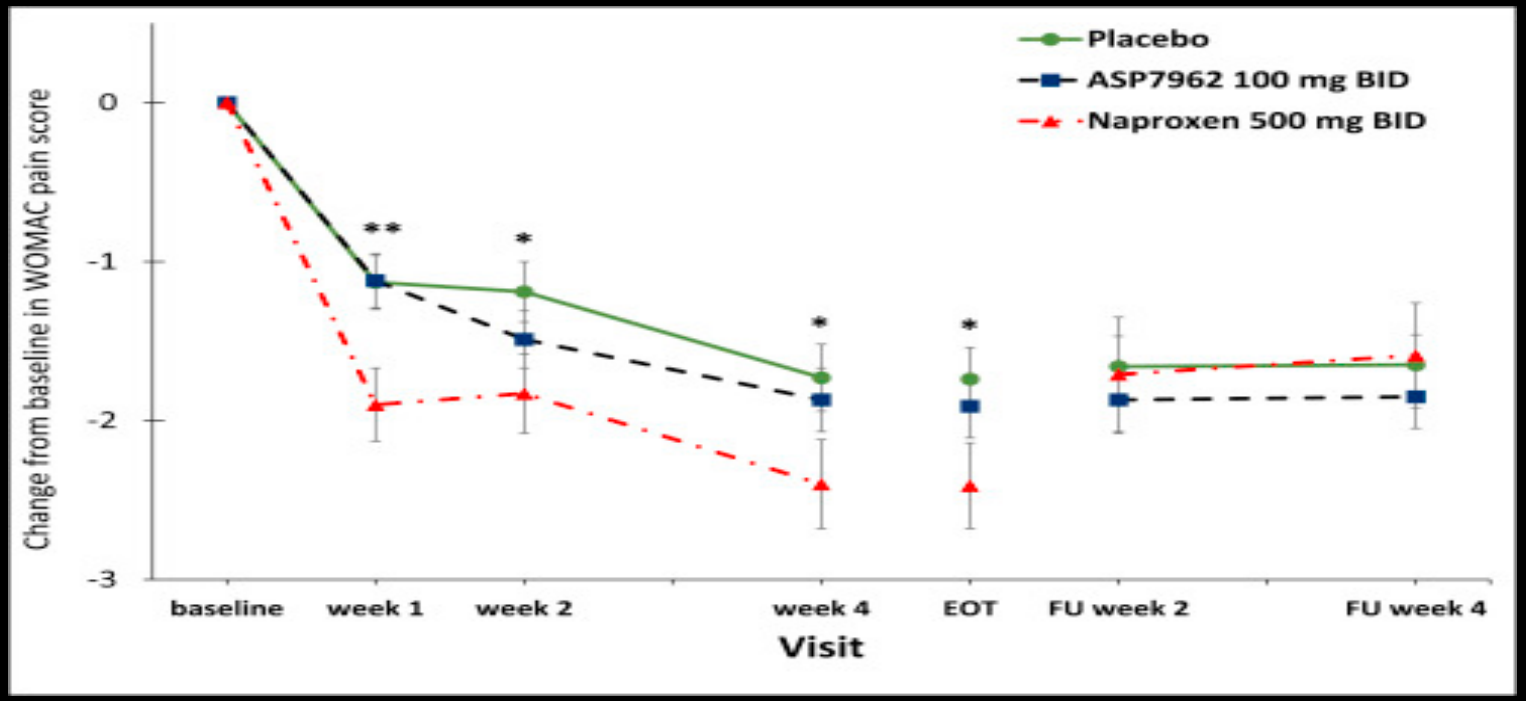
Tropomyosin-related kinase A (TrkA) inhibition for the treatment of painful knee osteoarthritis: results from a randomized controlled phase 2a trial

F.E. Watt, M.B. Blauwet, A. Fakhoury, H. Jacobs, R. Smulders, N.E. Lane

Osteoarthritis and Cartilage
Volume 27 Issue 11 Pages 1590-1598 (November 2019)
DOI: 10.1016/j.joca.2019.05.029

PAINWEEK

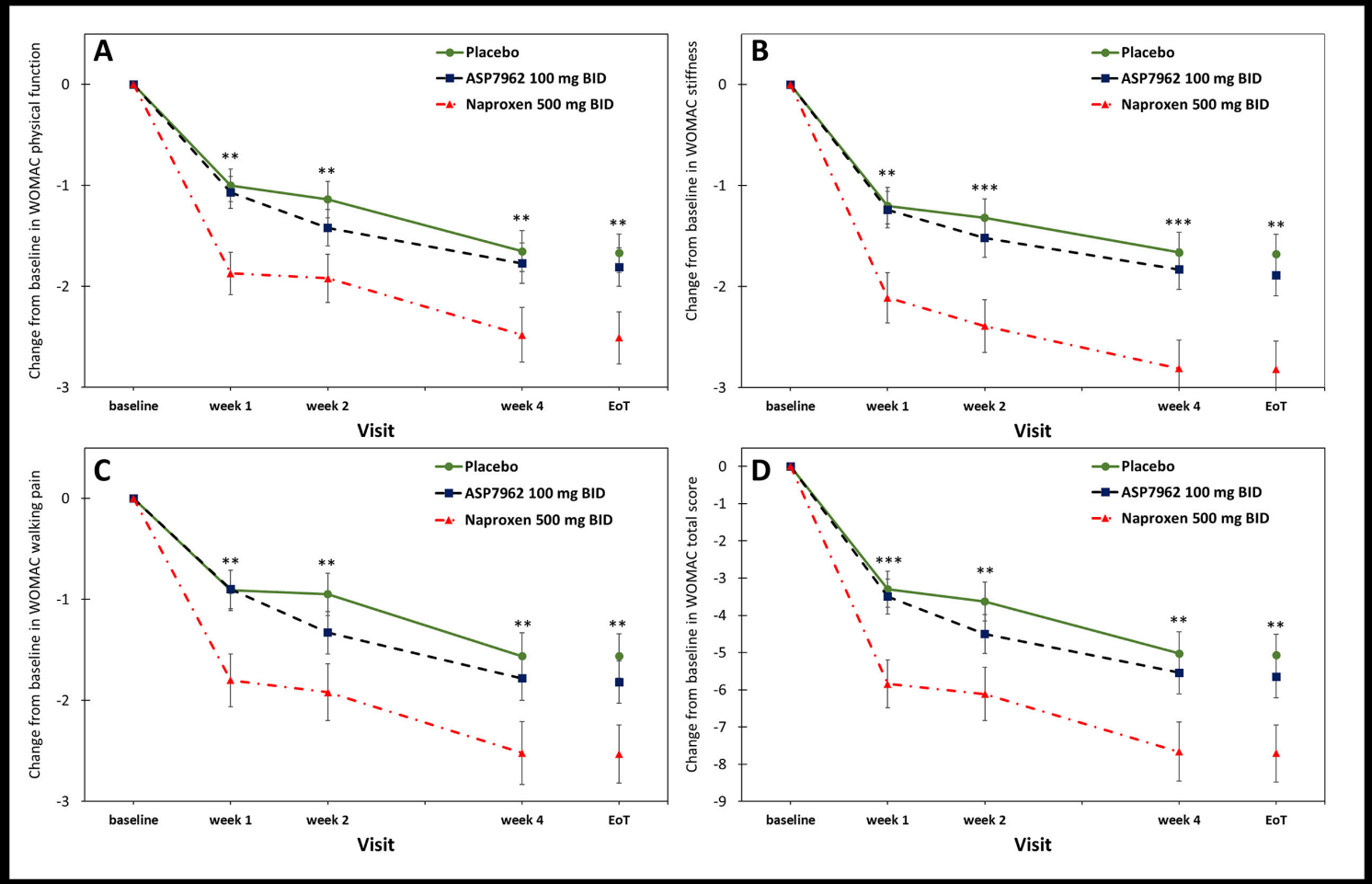
Change From Baseline and Follow-up in WOMAC Pain Subscale Score in the Index Knee



Watt F. et a O and C 2019

Fig. 3

Changes From Baseline in WOMAC Subscales (A–B), Walking Pain (C), and Total (D) Scores.



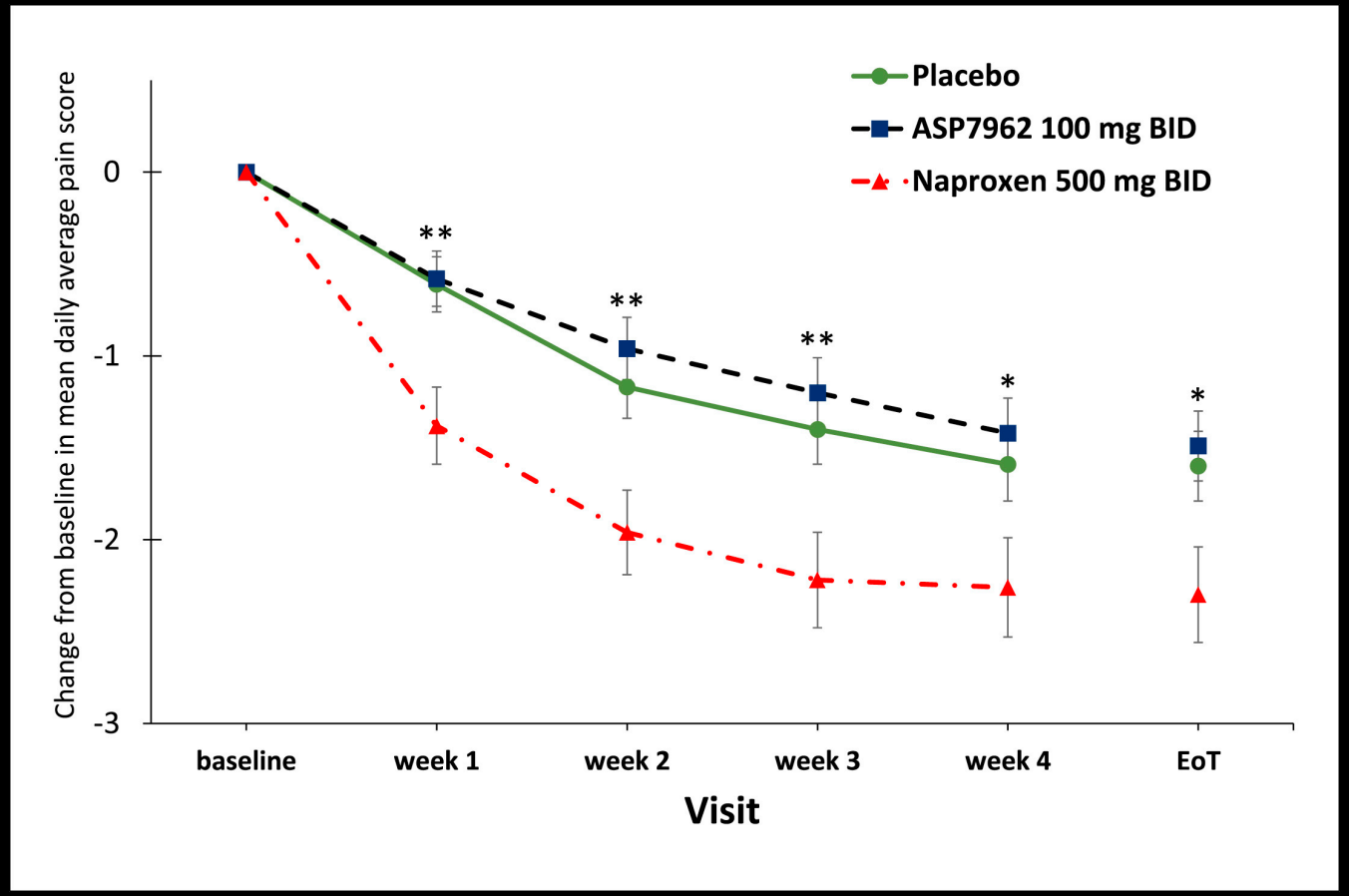
Watt F et al O and C. 2019

PainWeek®

Osteoarthritis and Cartilage 2019 271590-1598DOI: (10.1016/j.joca.2019.05.029)

Fig. 4

Change From Baseline in Mean Daily Average Pain Score in the Index Knee



Osteoarthritis and Cartilage 2019 271590-1598DOI: (10.1016/j.joca.2019.05.029)

Effects of Interleukin-1 Inhibition on Incident Hip and Knee. Replacement: 5 Exploratory analyses from a randomized, double-blind, placebo6 controlled trial

Annals of Internal Medicine. August 2020

Canakinumab (IL-1B inhibitor) , given SQ every 3 months for up to 5 years, reduced total knee and hip Replacements by over 50%, average duration of treatment of 3.4 years.

Conclusions

- A number of novel agents are in late stage development to prevent the progression of knee OA.
- A novel analgesic, anti-NGF, will provide long term pain relief for OA subjects
- The next few years should see significant progress in agents to prevent and treat this disabiling disease.