GENASCENCE

THE LEADER IN GENE THERAPY FOR JOINT DISEASES

JUNE 25, 2026

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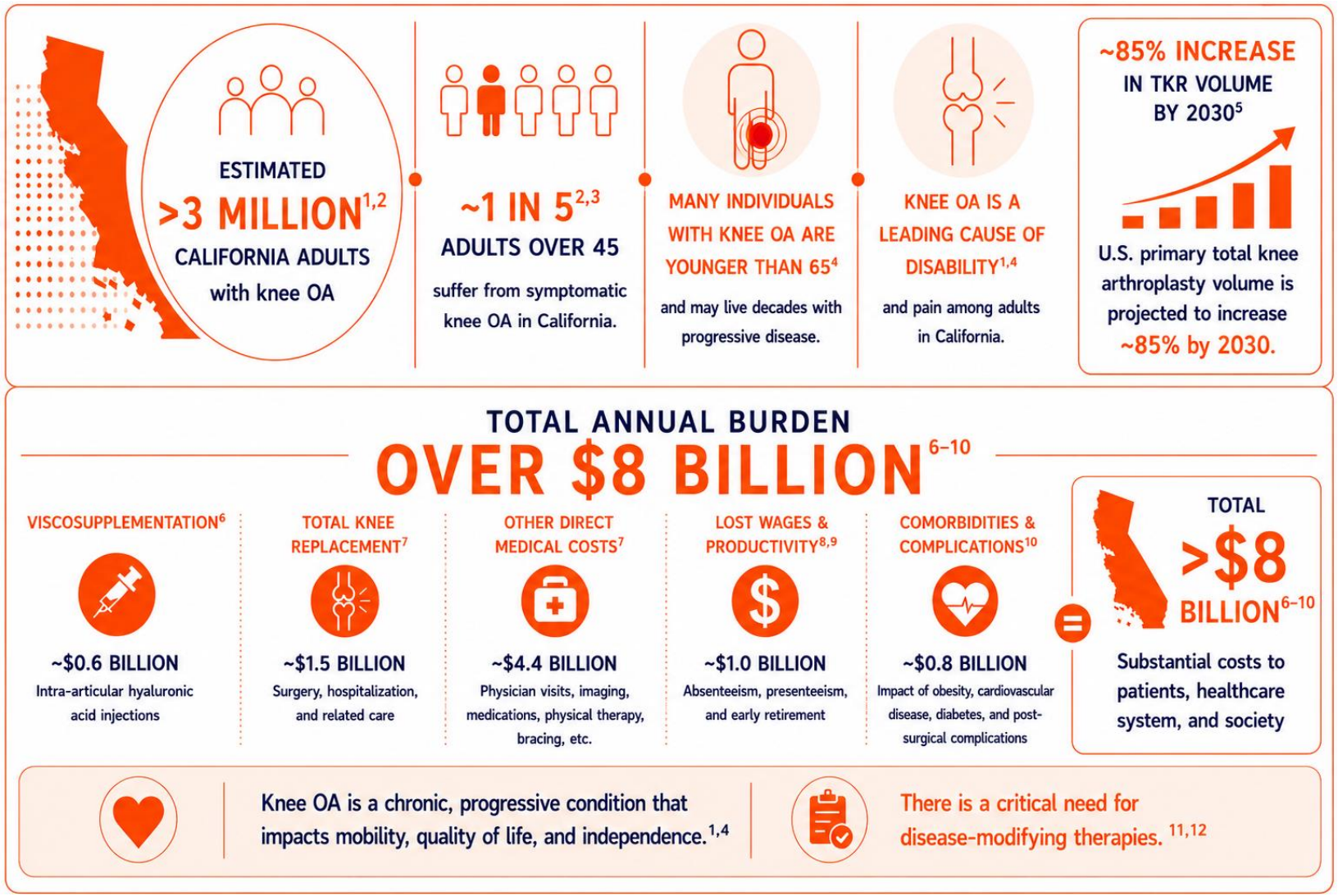
Knee Osteoarthritis Is a Highly Prevalent,
Disabling, Degenerative Disease Affecting Millions

New Therapies Urgently Needed for Californians Suffering From Knee OA



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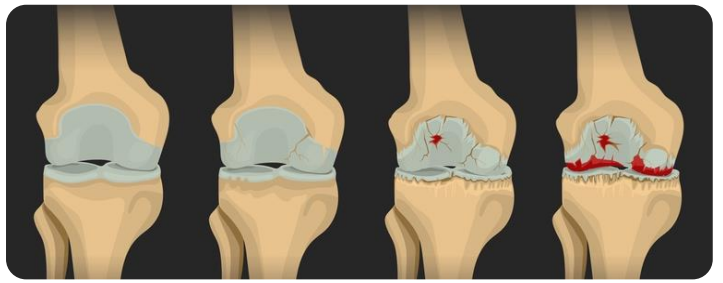
Knee Osteoarthritis (OA): Prevalent Chronic Disease with Significant Unmet Need

No Effective Treatments

Compromised pain/function
Nothing to delay/prevent joint replacement

NSAIDs, Tylenol,
Opioids,
Walking aids

Steroids: 4-12 weeks, no re-dosing
Hyaluronic acid: No/low benefit
Platelet-rich plasma: Low evidence



Total Knee Replacement 1.2M/ year in US; growing 7%[1,2] and 20-30% still have chronic pain[3]

Patients average 13 years of pain/disability with limited treatments[4]

Significant morbidity/mortality; #1 cause of disability; a top cause of chronic pain[5]

Existing treatments have significant safety concerns (black box warnings, addiction)[6-8]

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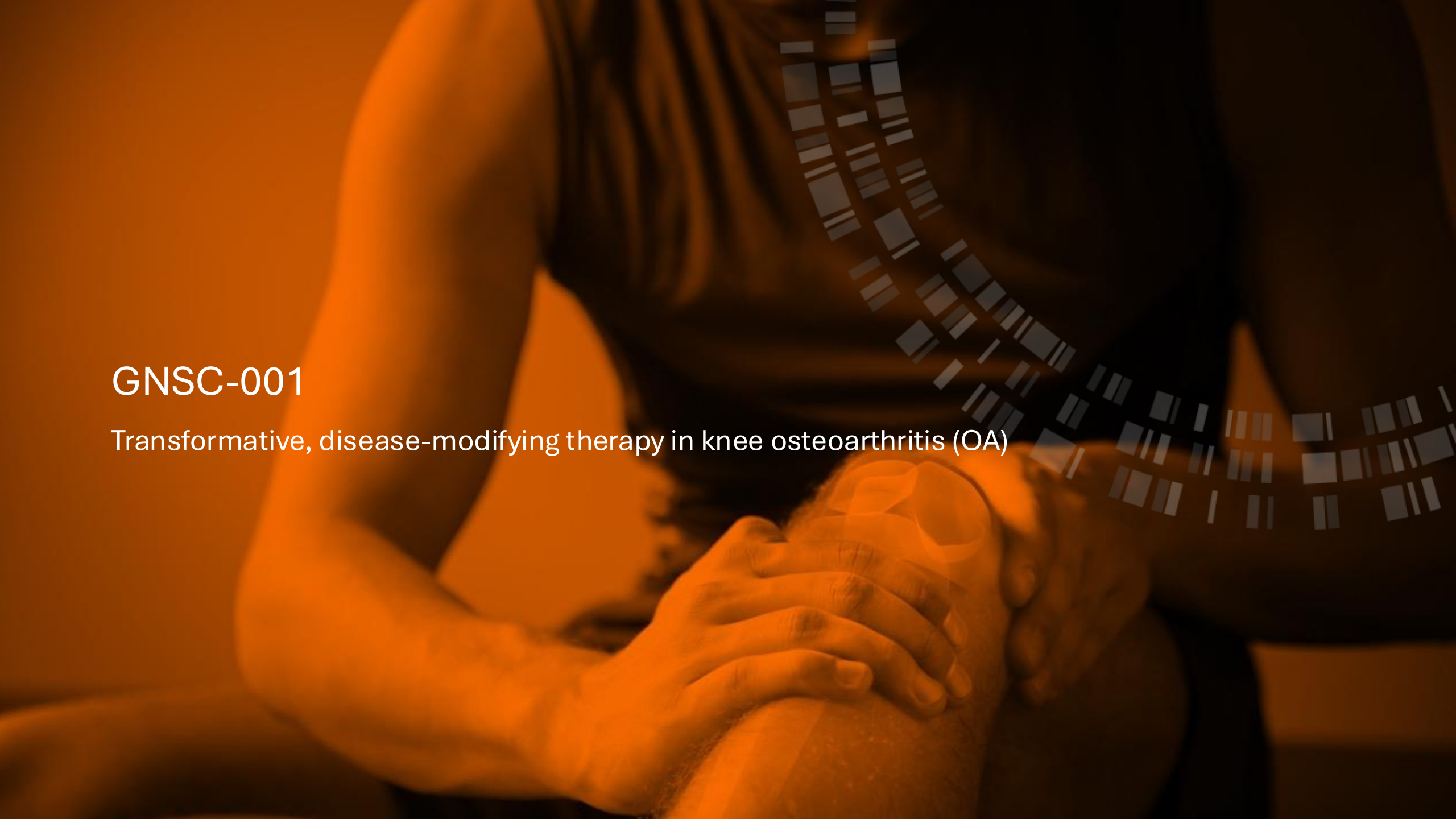
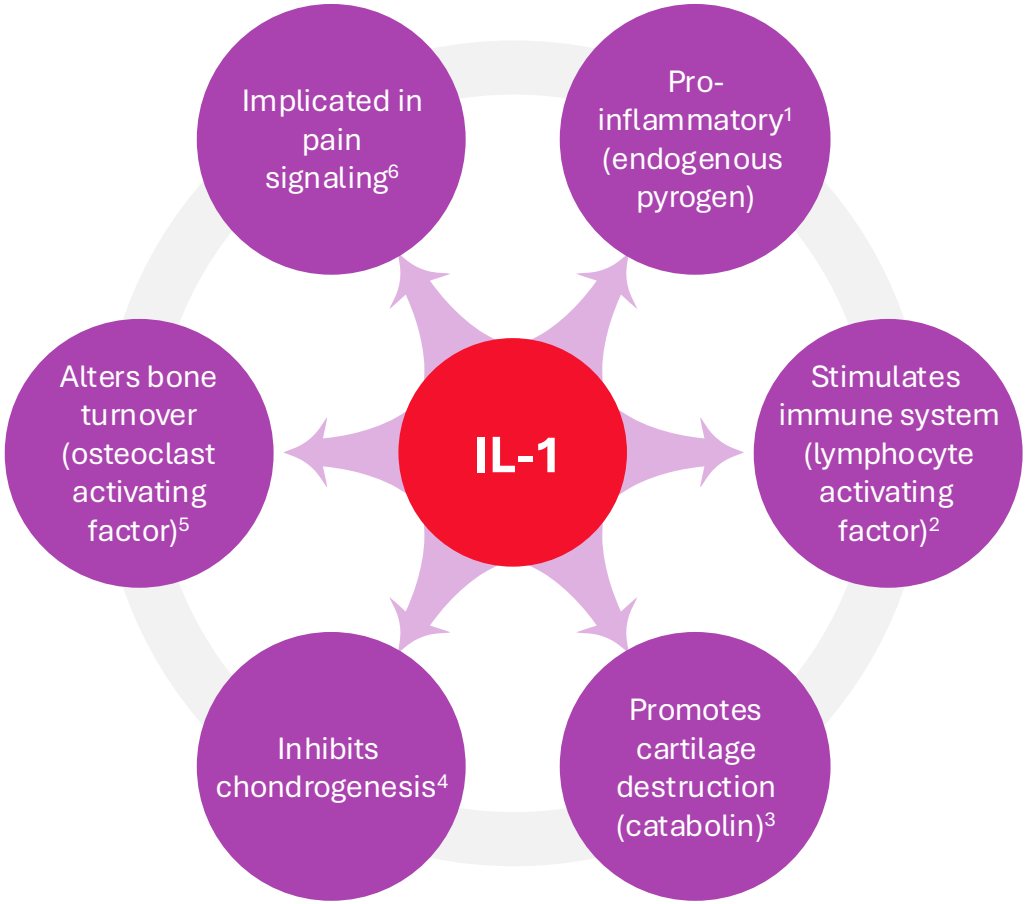


GNSC-001

Transformative, disease-modifying therapy in knee osteoarthritis (OA)

IL-1 Plays a Central Role in OA Inflammation, Pain, and Disease Progression

Evidence from biochemical studies, human genetics, clinical trials, and Genascence's own data support IL-1 as a critical target for both pain and disease progression in OA




ARTHRITIS & RHEUMATISM
Vol. 46, No. 6, June 2002, pp 1519–1527
DOI 10.1002/art.10260
© 2002, American College of Rheumatology

Association of the Interleukin-1 Gene Cluster on Chromosome 2q13 With Knee Osteoarthritis

John Loughlin, Barbara D

www.impactjournals.com/oncotarget/ Oncotarget, 2017, Vol. 8, (No. 3), pp: 4228-4233

Research Paper

IL1R1 gene polymorphisms are associated with knee

lan population

an Wei[1], Daihe Li[1], Yong Wang[1], Chao [1,4] and Wanlin Liu[1]

Rheumatol Int (2012) 32:2135–2141
DOI 10.1007/s00296-011-1946-3

ORIGINAL ARTICLE

IL1B -511(G>A) and IL1RN (VNTR) allelic polymorphisms and susceptibility to knee osteoarthritis in Croatian population

Zdravko Jotanovic · Godfrey Essien Etokebe · Radovan M
Marikken Heiland Kaarvatn · Biserka Mulac-Jericevic · T
Sanja Balen · Branko Sestan · Zlatko Dembic

Interleukin 1 receptor antagonist (*IL1RN*) gene variants predict radiographic severity of knee osteoarthritis and risk of incident disease

Mukundan Attur [1], Hua Zhou,[2] Johathan Samuels,[1] Svetlana Krasnokutsky,[1] Michelle Yau,[3] Jose U Scher,[1] Michael Doherty,[4] Anthony G Wilson [5],

anne M Jordan,[8] Braxton Mitchell,[7,9]

doi:10.1136/annrheumdis-2019-216055

The Journal of Infectious Diseases

IDSA Infectious Diseases Society of America hivma hiv medicine association OXFORD

Interleukin-1 Receptor Antagonist Gene (*IL1RN*) Variants Modulate the Cytokine Release Syndrome and Mortality of COVID-19

Mukundan Attur,[1,4,8] Christopher Petrilli,[2,4] Samrachana Adhikari,[3,4] Eduardo Iturrate,[2] Xiyue Li,[3] Stephanie Tuminello,[3] Nan Hu,[4] Aravinda Chakravarti,[2,4] David Beck,[2,4] and Steven B. Abramson[2,9]

[1]Division of Rheumatology, Department of Medicine, New York University Langone Orthopedic Hospital, New York University Langone Health, New York, New York, USA; [2]Department of Medicine, New York University Grossman School of Medicine, New York University Langone Health, New York, New York, USA; [3]Division of Biostatistics, Department of Population Health, New York University Grossman School of Medicine, New York, New York, USA; and [4]Center for Human Genetics and Genomics, New York University Grossman School of Medicine, New York, New York, USA

1. Dinarello, CA., Blood, 2011; 117(14): 3720-3732.
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3. Hubbard *et al., J Orthop Res.*, 1988; 6:180-7.
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Previous Attempts to Target IL-1 Have Been Mixed Because Drug Delivery to Joints is Challenging

Intra-articular delivery:

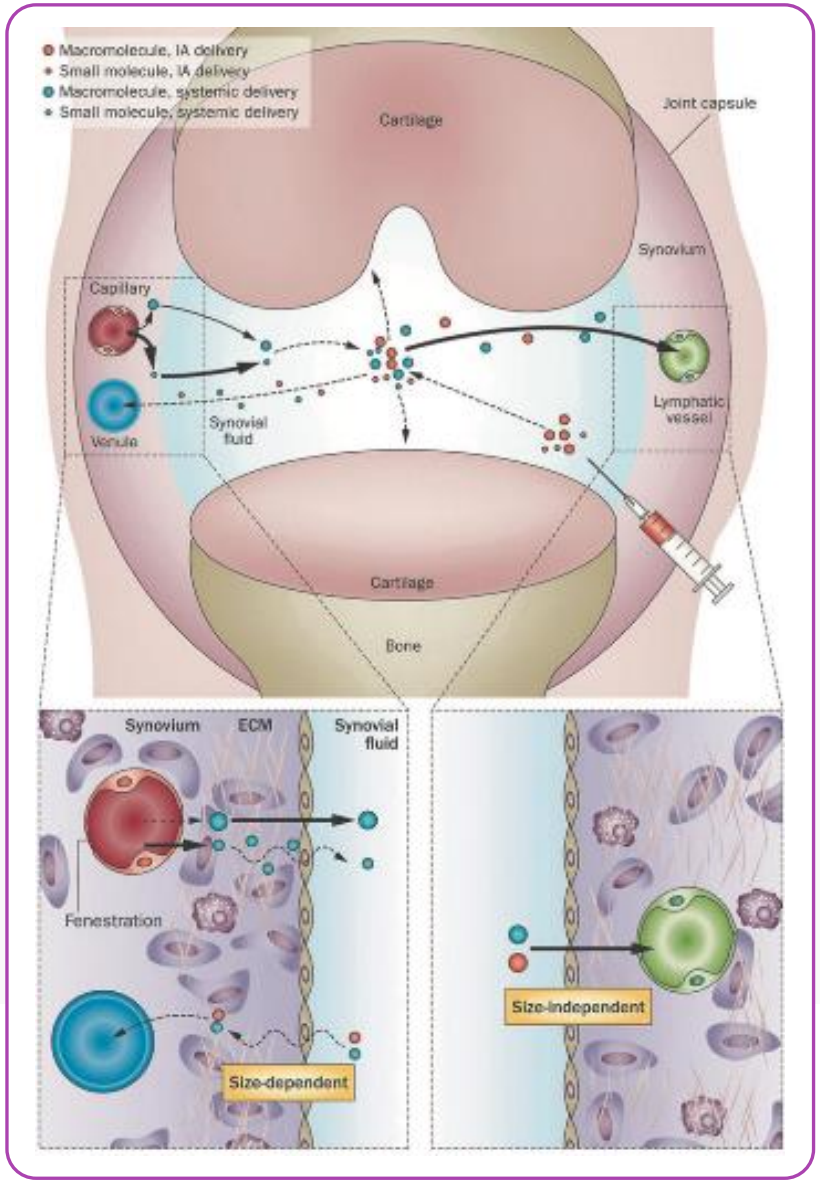
Rapid efflux from joints (hours)

Initial attempts with anakinra effective at Day 4 but not long term[1]

Systemic delivery:

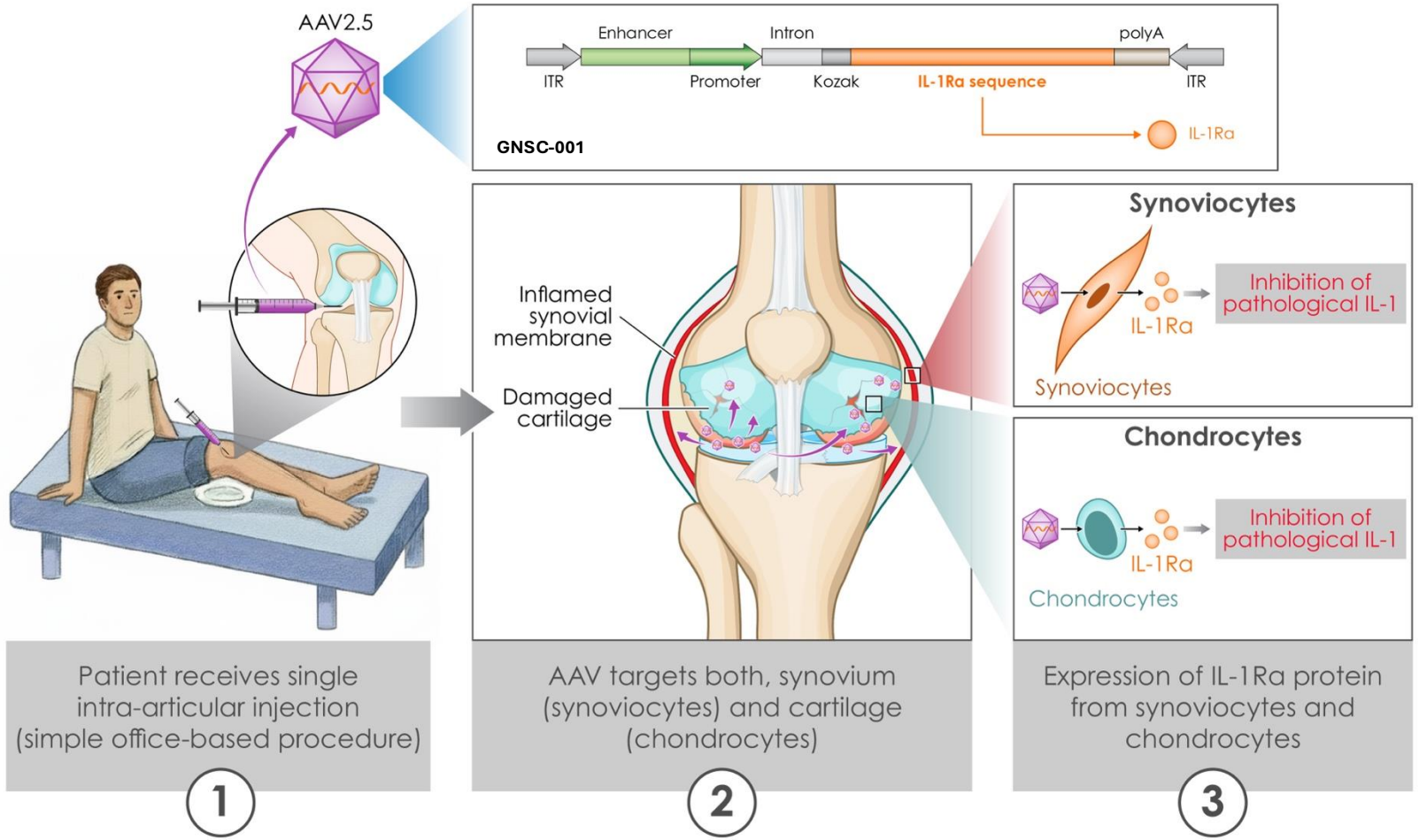
Systemic side effects (neutropenia, infections) and limited/variable penetration into cartilage

Multiple studies showing trends in pain and lower TKR rates with systemic IL-1 inhibitors[2,3]

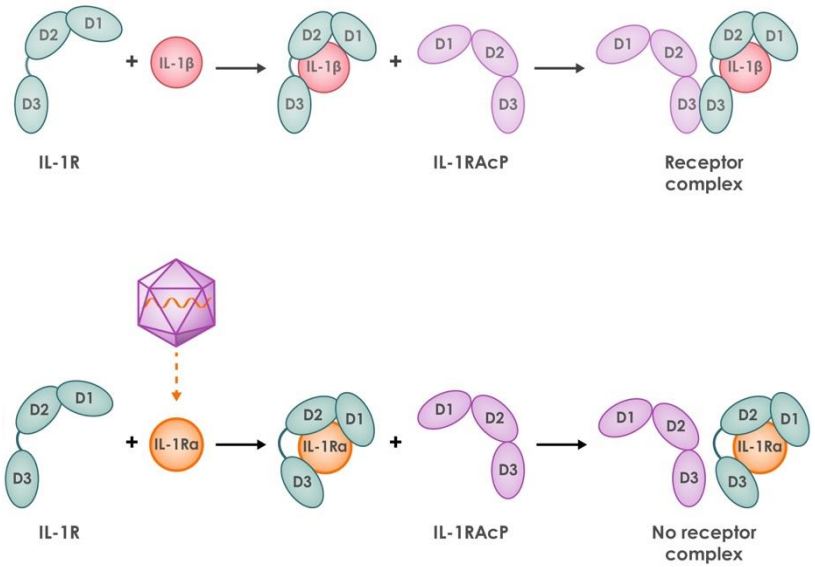


1. Chevalier et al. Arthritis Rheum. 2009 Mar 15;61(3):344-52. doi: 10.1002/art.24096.
2. Shieker M, *et al.*, Annal. Int. Med. 2020; 173(7): 509-515.
3. Heijman *et al.*, Annal. Int Med, 2023; 176(6): https://doi.org/10.7326/M23-0289

GNSC-001: “Biofactory” Produces Therapeutic Protein Deep Within Joints



Blockade of IL-1 signaling with IL-1Ra (IL-1 receptor antagonist)



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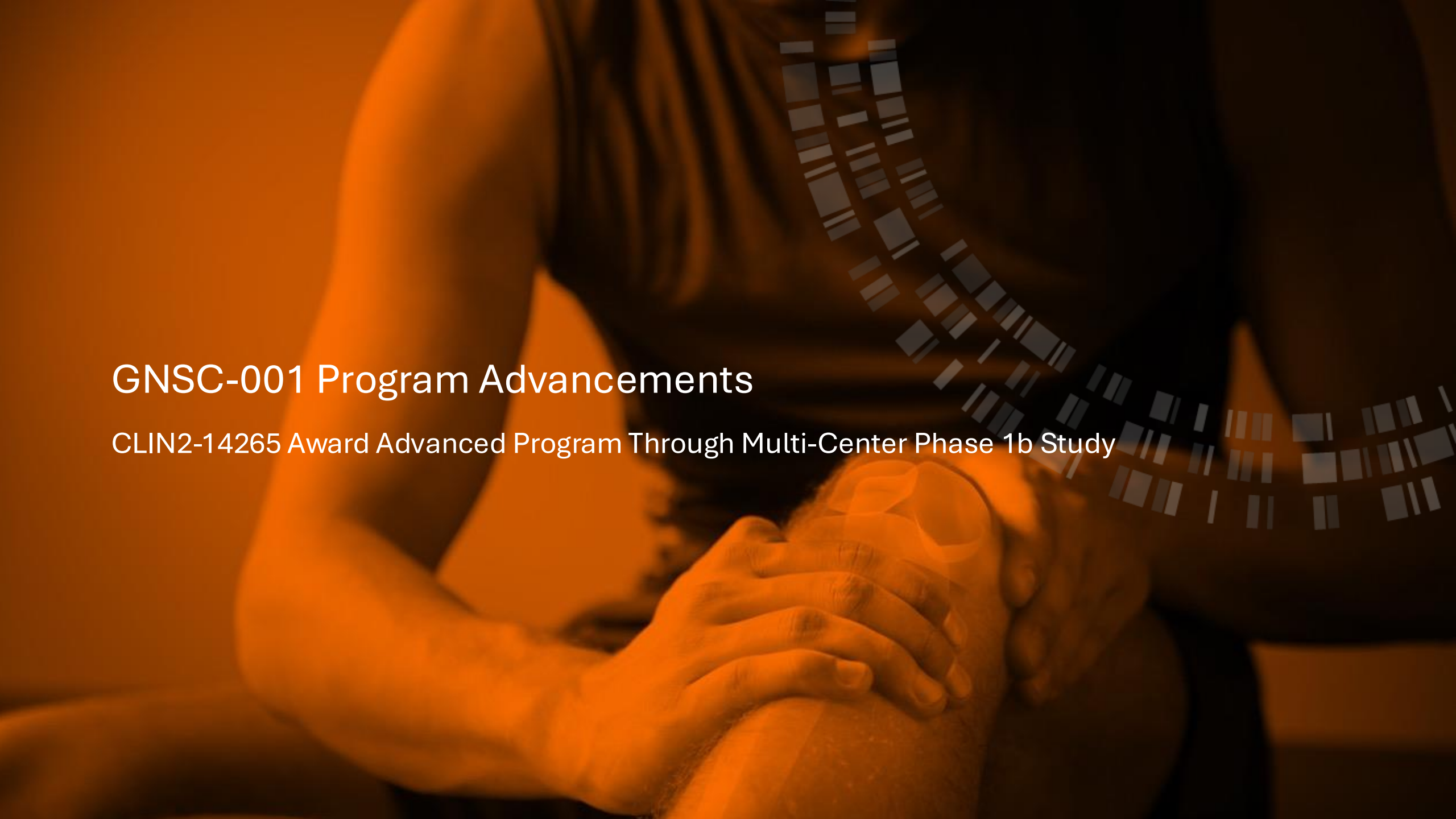


GNSC-001 Program Advancements

CLIN2-14265 Award Advanced Program Through Multi-Center Phase 1b Study

Overview of GNSC-001 Clinical Development Program

15-007542

Phase 1 (n=9)
Investigator-Sponsored
Single Ascending Dose
First-in-Human study

Well-tolerated;
No product-related SAEs

DONATELLO

Phase 1b (n=67)
Company-Sponsored
Safety, Dose-Ranging ± Immune Conditioning

Well-tolerated;
Robust IL-1Ra expression

RAPHAEL

Phase 2/3
(n=240)
Primary EP: Pain/Function
Secondary EP: Structural

Planned Initiation
2027

Series A funding
CLIN-2 Award

Series B funding
Potential for additional CIRM support

DONATELLO Phase 1b Study Design: Dose-Ranging and Pharmacodynamics

DONATELLO

Objectives:

Determine safety and dose for further development

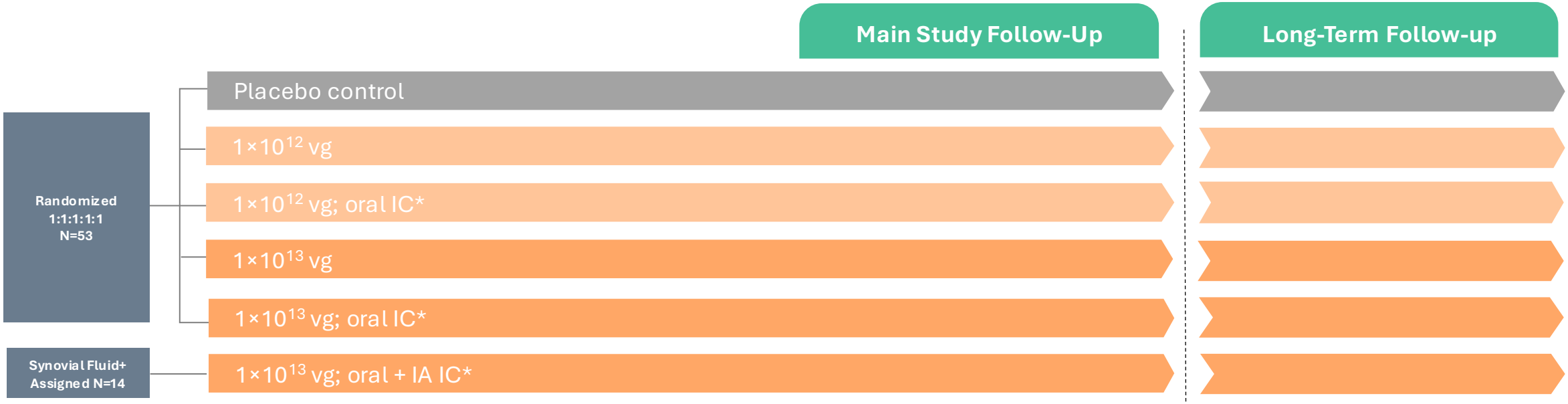
Investigate potential role for immune conditioning (IC)

Endpoints:

Primary: Safety

Key Secondary: IL-1Ra levels in synovial fluid

Exploratory: Patient reported outcomes, immune responses



* Immune conditioning

BL = baseline; M = month; IA = interim analysis; 1°EP = primary endpoint

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Manufacturing Improvements Yielded Scalable, Commercially Viable Process

Upstream Production

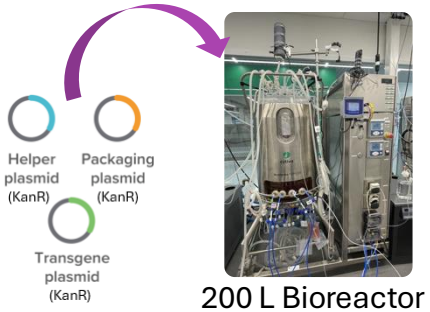
Downstream Production

Pre-Change

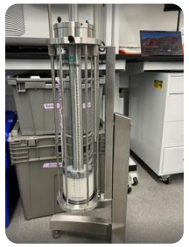
36-Layer HYPERStacks (adherent culture)

Ultracentrifugation

Post-Change



200 L Bioreactor (suspension culture)



Affinity Chromatography

AEX Chromatography

Final TFF

New Process Advantages

- GMP suitable critical reagents
- Highly scalable
- Increased productivity
- Comparable percentage full capsids
- Commercially viable COGS

Reached agreement with FDA on new manufacturing process for GMP drug to be used in next clinical trial

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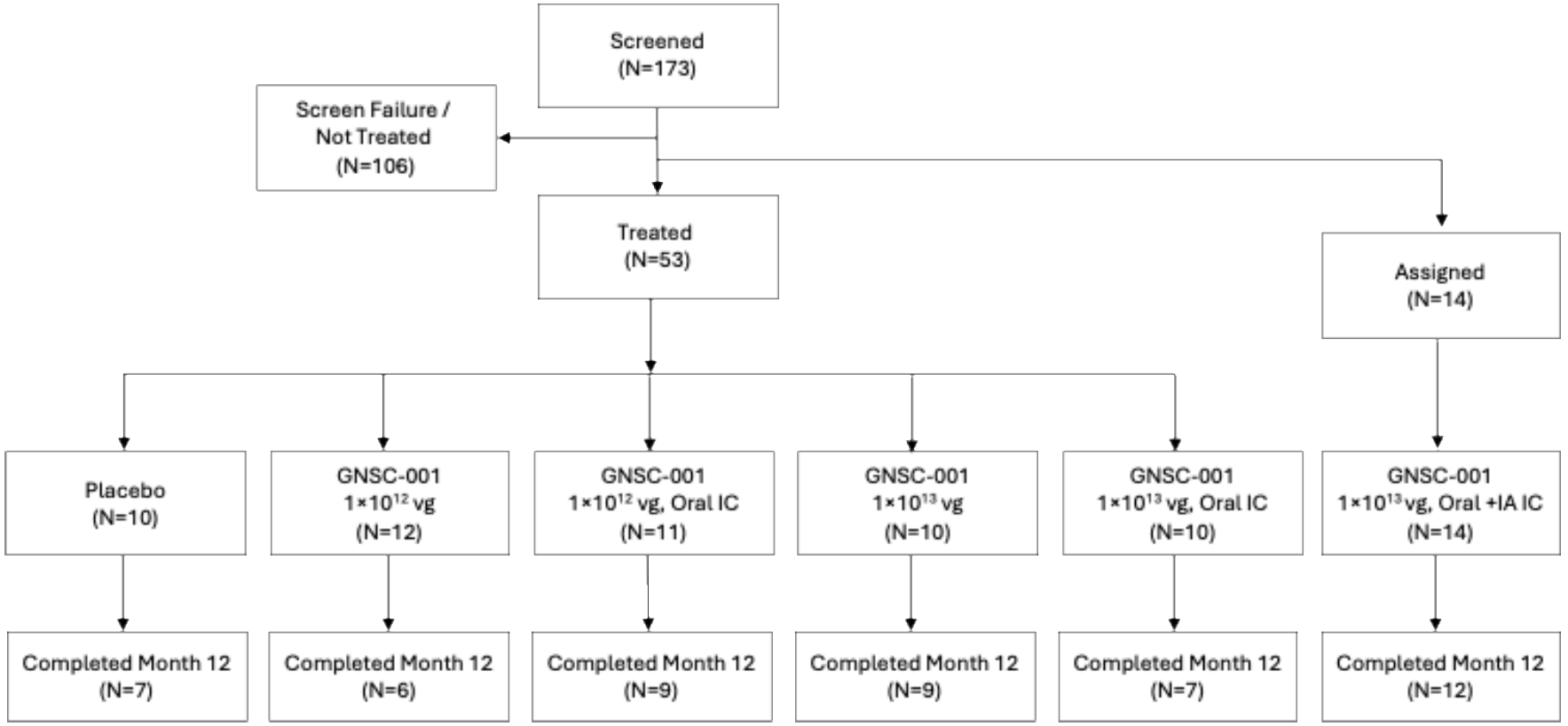
Phase 1b DONATELLO Study Met Study Objectives and Provided Encouraging Early Results

DONATELLO Enrolled and Treated 67 Participants at 9 Clinical Sites



Participants were reflective of California OA population in age, gender, and race

BASELINE CHARACTERISTICS

Age in years: Mean (SD)	60.9 (8.5)
Gender	
• Male	15 (22.4%)
• Female	52 (77.6%)
BMI: Mean (SD)	28.6 (4.3)

RACE

• American Indian	1 (1.5%)
• Black or African American	8 (11.9%)
• White	50 (74.6%)
• More than One Race	3 (4.5%)
• Not reported/Other	5 (7.5%)

ETHNICITY

• Hispanic or Latino	11 (16.4%)
• Not Hispanic or Latino	54 (80.6%)
• Not Reported	2 (3.0%)

Primary Endpoint: Favorable Safety and Tolerability Profile

DONATELLO

TEAEs: No liver enzyme elevation, changes in blood counts/ biochemistry, or signs of systemic IL-1 suppression. AEs were primarily CTCAE Grade 1-2, with no treatment-related deaths or SAEs.

DONATELLO	Groups 1-5 (n=53); Randomized					Group 6 (n=14); SF+; Assigned
Related Target Knee Adverse Events (TKAEs)	**Placebo**	**GNSC-001 (1×10^{12} vg)**	**GNSC-001 (1×10^{12} vg; oral IC)**	**GNSC-001 (1×10^{13} vg)**	**GNSC-001 (1×10^{13} vg; oral IC)**	**GNSC-001 (1×10^{13} vg; oral+IA IC)**
	(N=10)	(N=12)	(N=11)	(N=10)	(N=10)	(N=14)
No. of subjects with ≥1 related TKAE	1 (10.0%)	1 (8.3%)	1 (9.1%)	2 (20.0%)	2 (20.0%)	7 (50.0%)
No. of related TKAEs	1	1	1	2	2	15
Patients (%) with at least 1 AE of:						
Arthralgia	0 (0.0%)	0 (0.0%)	1 (9.1%)	1 (10.0%)	2 (20.0%)	4 (28.6%)
Joint Swelling	0 (0.0%)	1 (8.3%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	3 (21.4%)††
Joint Effusion	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (14.3%)
Joint Stiffness	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	2 (14.3%)
Arthritis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)
Bursitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)
Injection site joint pain/discomfort	1 (10.0%)	0 (0.0%)	0 (0.0%)	2 (20.0%)	1 (10.0%)	0 (0.0%)
Injection site hemorrhage	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)
Injection site reaction	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)

TKAEs: Predominantly mild/moderate; only 1 Grade 3 (knee effusion) in Group 6.
Higher trend in Group 6 may relate to enrolling only synovial fluid+ population.
Overall, well-tolerated and "as expected" at all dose levels and consistent with TPP.

†† Grade 3 AE was a recurring joint effusion in a single patient, deemed by investigator to be treatment-related; subject had knee fracture and OCF on MRI.

Secondary Endpoint: Target Levels of IL-1Ra Expressed Long-Term Following Single, Local Injection

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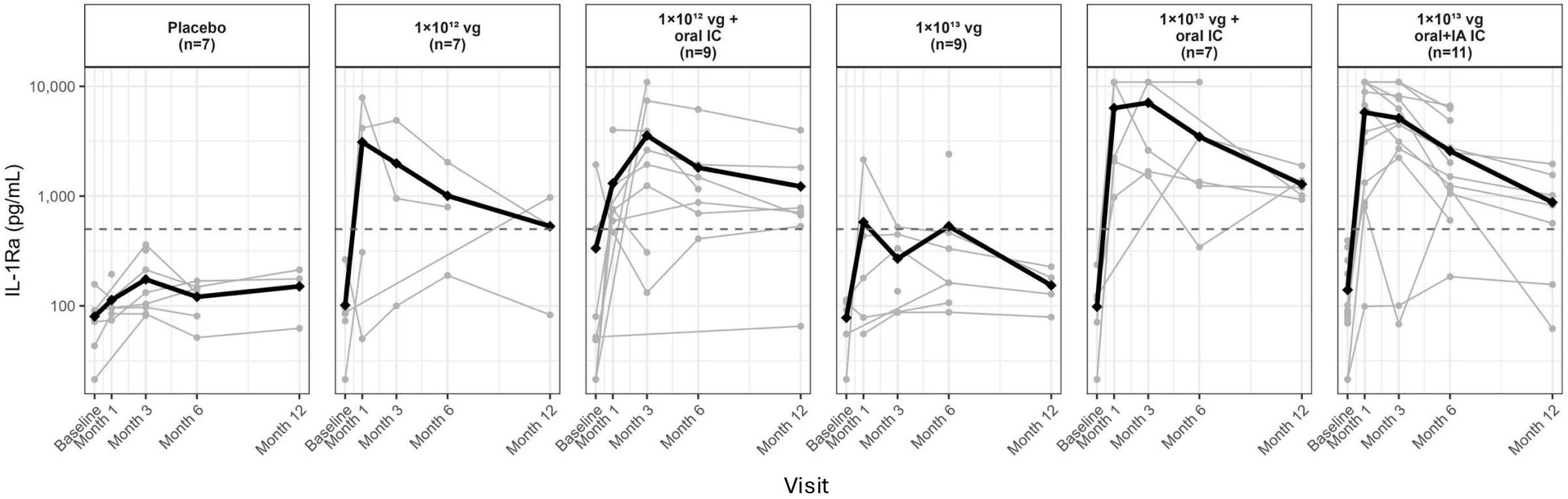

IL-1Ra expression at/above therapeutic levels observed in most GNSC-001-treated participants for >12 months

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Exploratory Endpoint: NRS Pain [0-10] – Encouraging Trend in Pain Reduction Noted in GNSC-001-Treated Groups at 12-month Timepoint

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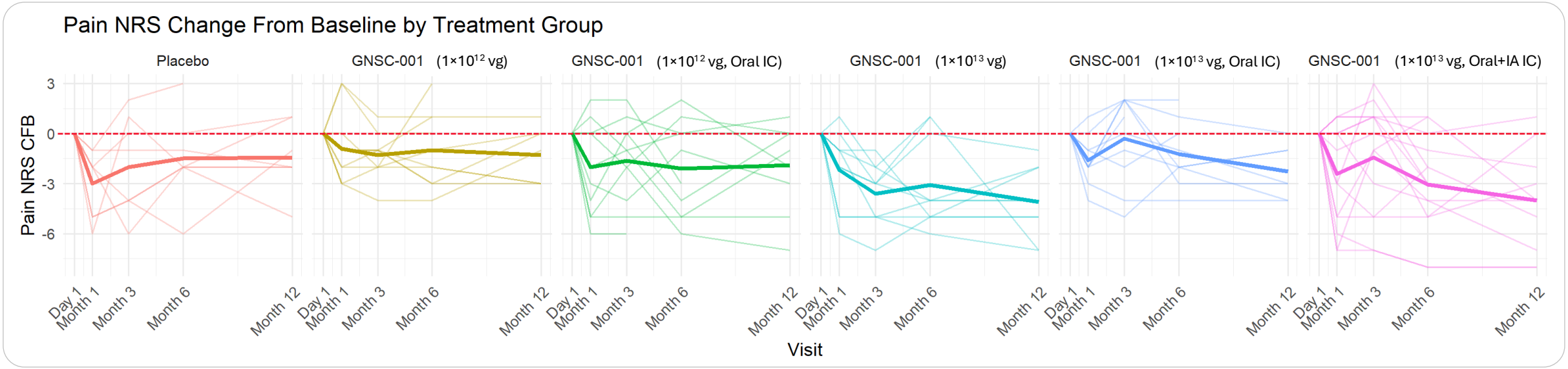

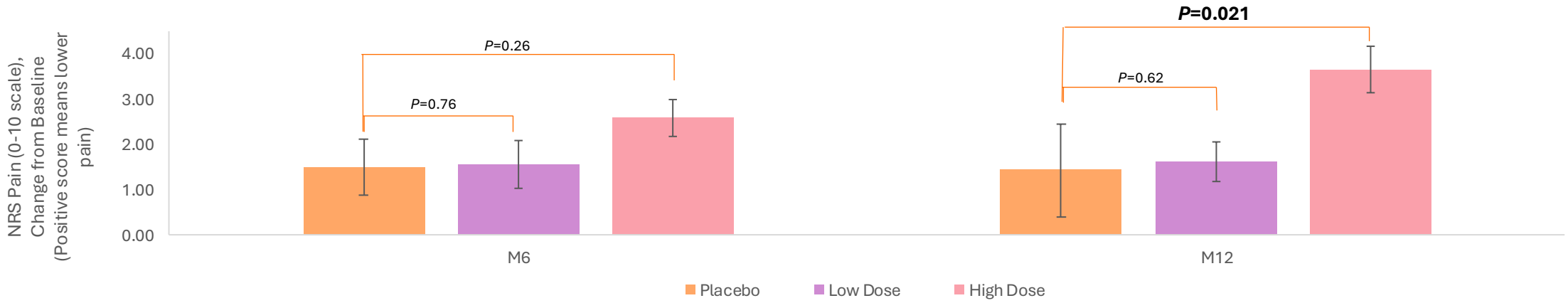

Although study was not designed / powered to measure pain outcomes, encouraging responses observed

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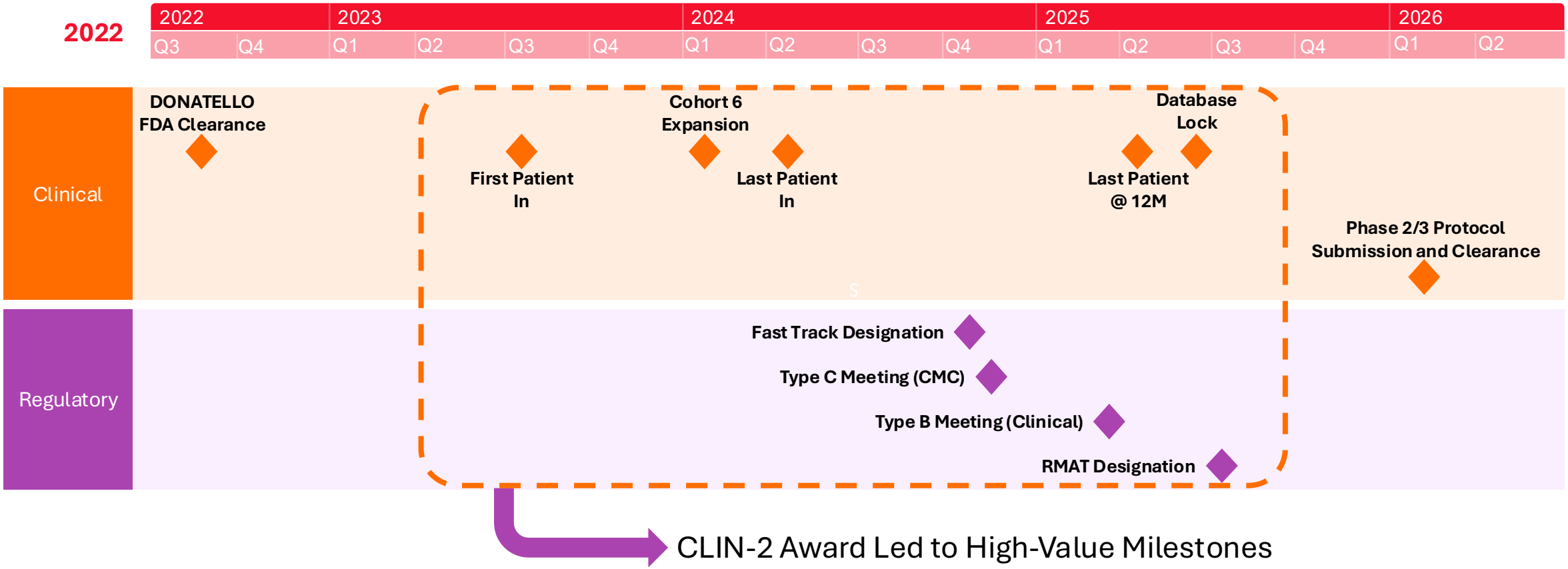
DR. SUSAN BUKATA
UC SAN DIEGO | DONATELLO INVESTIGATOR

Looking Forward: Bringing GNSC-001 to Patients in Need

Phase 2/3 Trial Creates a Path to Registration

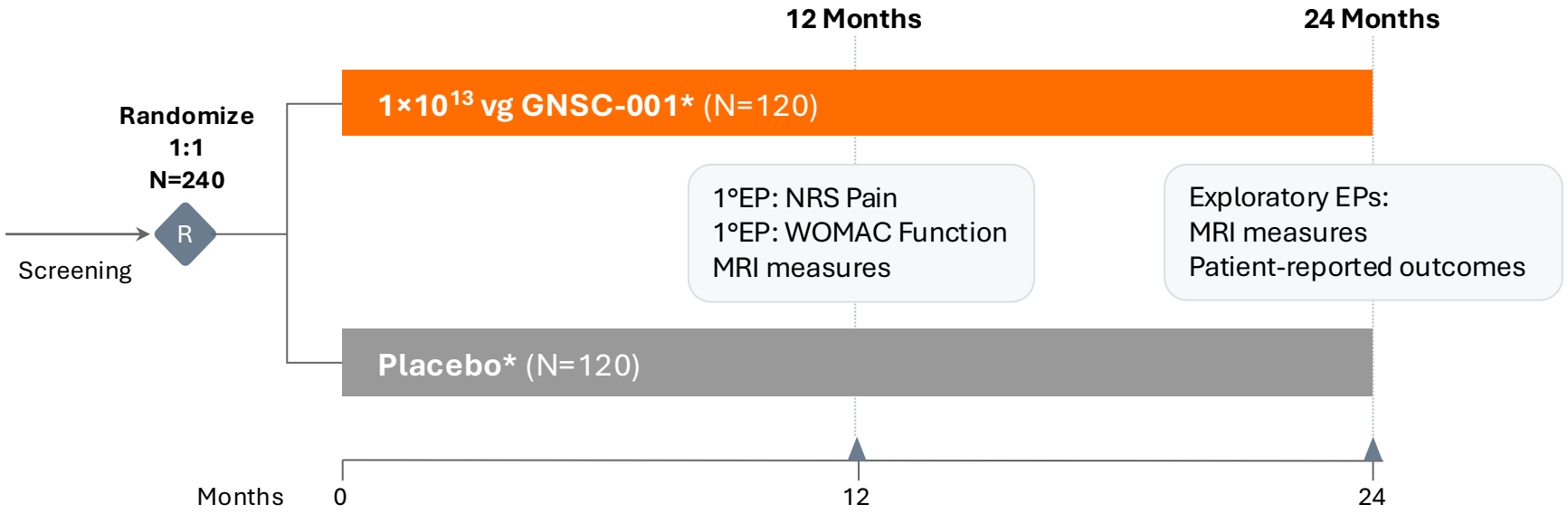
Program Milestones Show Continued Momentum in Clinical and Regulatory



Phase 2/3 RAPHAEL Study Focused on Clinical and Structural Outcomes

Study Population

Target knee OA KL 2/3
Symptomatic (pain/function)



Objectives

Primary:
Evaluate change in pain / function at 12M
Safety outcomes: AEs, TKAEs

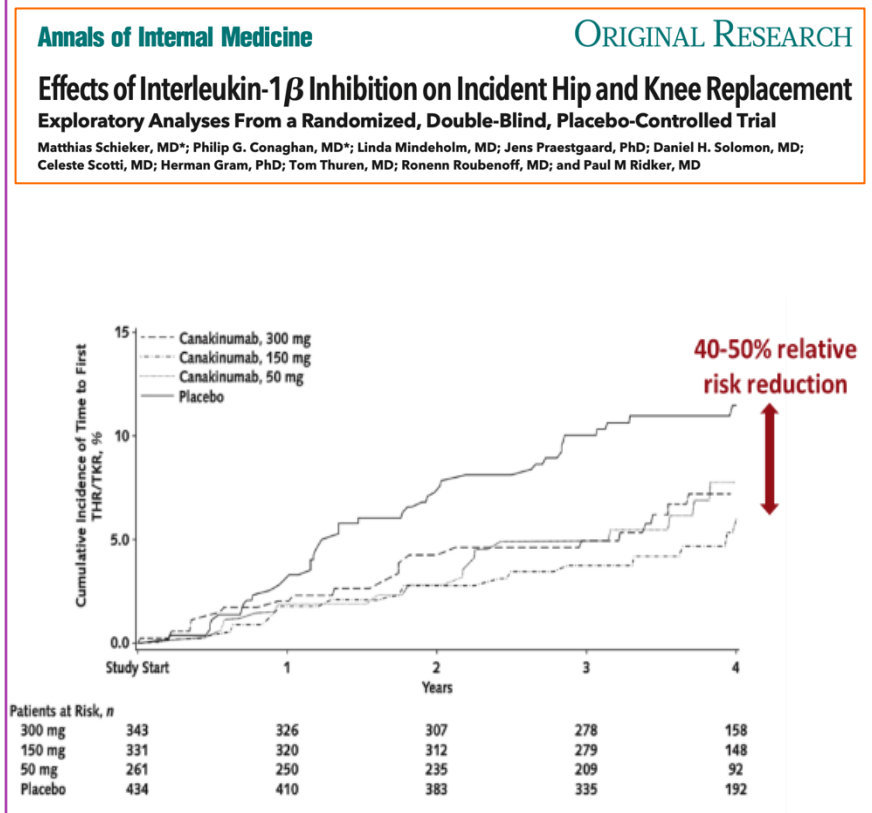
Secondary / Exploratory:
Disease progression (MRI) at 12/24M
Clinical outcomes at 12/24M

Other:
Potential extension study for long-term follow up

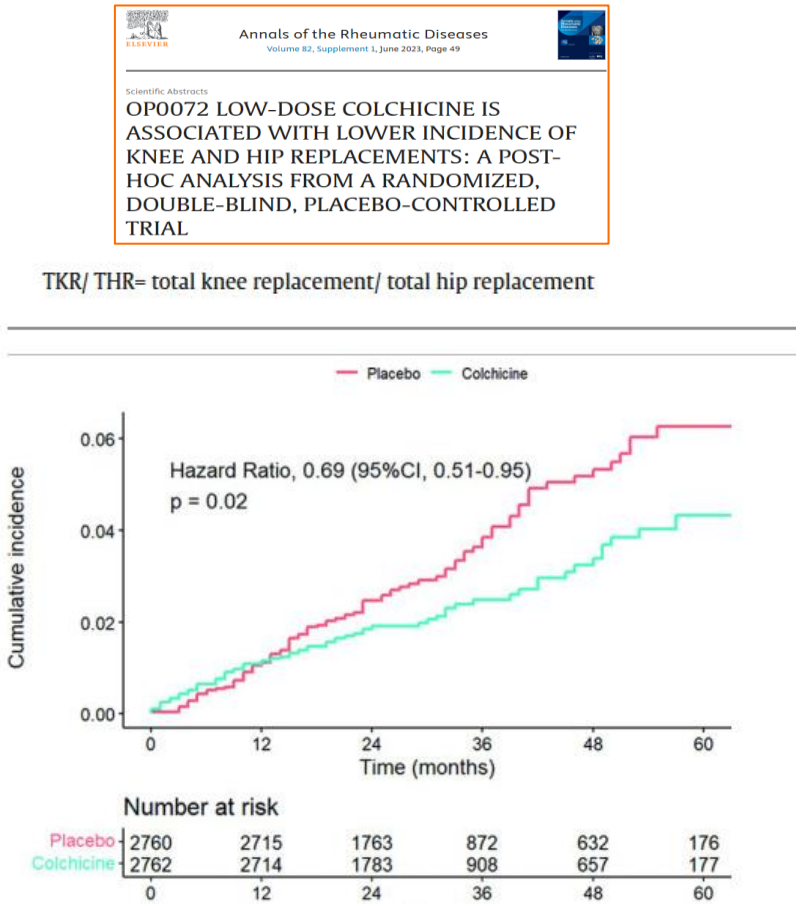
* All groups to receive identical, brief oral plus single IA immune-conditioning regimen

Clinical Studies with IL-1 Inhibitors Show Delay/Avoidance of TKR

CANTOS[1]: Cardiovascular study; patients with OA (n=1369) had less progression to joint replacement



LoDoCo2[2]: In large (n=5522) CV patient trial, colchicine arm showed significant reductions in joint replacements



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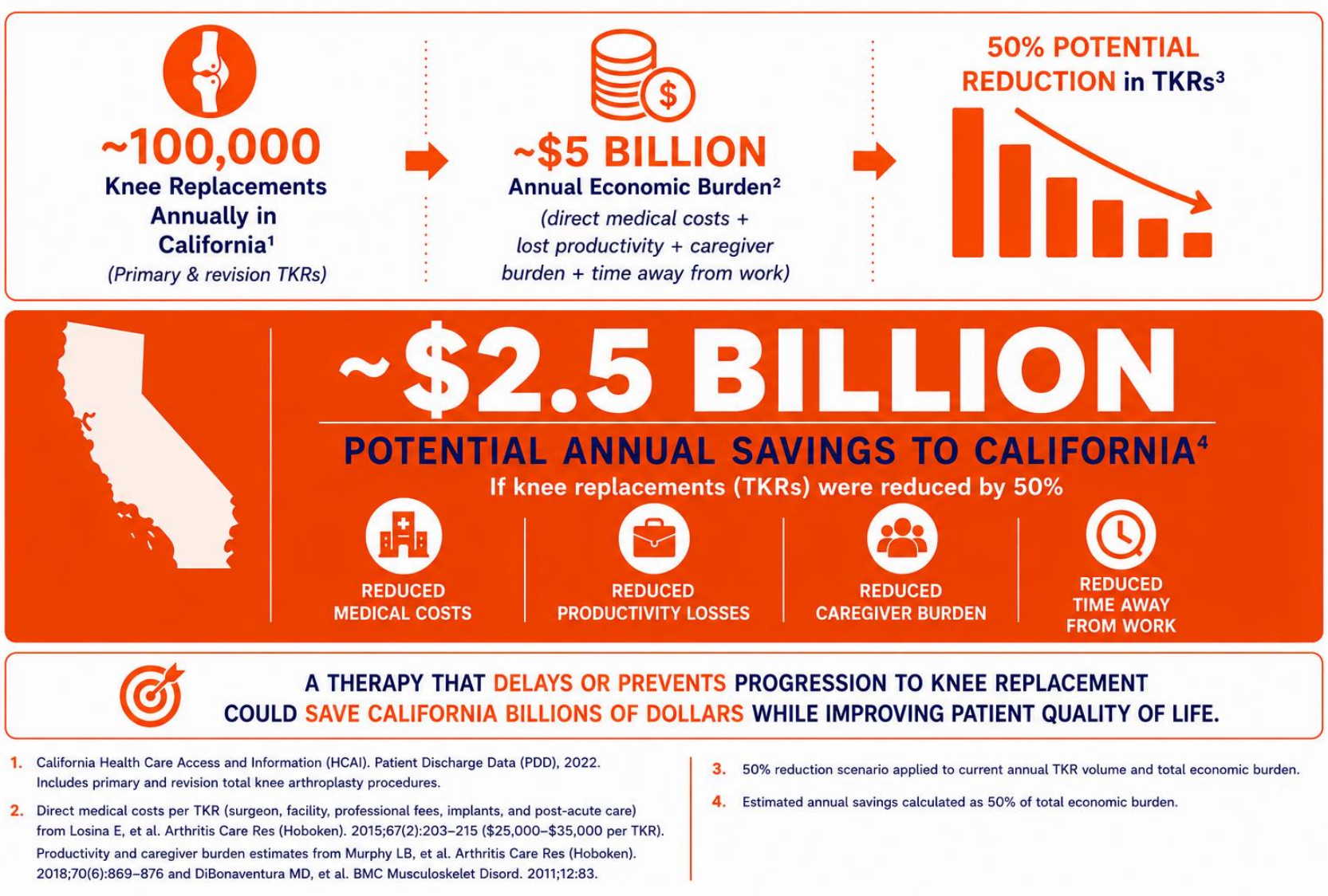
1. Shieker M, *et al.*, Annal. Int. Med. 2020; 173(7): 509-515.
2. Heijman *et al.*, Annal. Int Med, 2023; 176(6): https://doi.org/10.7326/M23-0289

Savings Potential in Knee Replacement Reduction



1. California Health Care Access and Information (HCAI). Patient Discharge Data (PDD), 2022. Includes primary and revision total knee arthroplasty procedures.
2. Direct medical costs per TKR (surgeon, facility, professional fees, implants, and post-acute care) from Losina E, et al. Arthritis Care Res (Hoboken). 2015;67(2):203–215 ($25,000–$35,000 per TKR). Productivity and caregiver burden estimates from Murphy LB, et al. Arthritis Care Res (Hoboken). 2018;70(6):869–876 and DiBonaventura MD, et al. BMC Musculoskelet Disord. 2011;12:83.
3. 50% reduction scenario applied to current annual TKR volume and total economic burden.
4. Estimated annual savings calculated as 50% of total economic burden.

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Summary & Thank You

GNSC-001 is a promising treatment for knee OA,
which has no FDA-approved therapies beyond pain management,
has disease-modifying potential to alleviate suffering,
and save billions in California healthcare costs

Thank you:

- DONATELLO Participants and Investigators
- Study Team
- CIRM and Genascence investors

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www.genascence.com