A Phase 3, 56-Week, Multicenter, Randomized, Double-Blind, Placebo Controlled Trial (OA-11) to Evaluate the Efficacy and Safety of a Single Injection of Lorecivivint Injected in the Target Knee Joint of Moderate to Severe Osteoarthritis Participants

STRIDES—X-ray

SM04690 Trial Evaluating a Randomized Injection for Determination of Efficacy and Safety

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Disclosures

- T. McAlindon:
  - Consultant and Investigator, Biosplice Therapeutics,
  - Consultant: Kolon TissueGene, Organogenesis, Remedium-Bio, Medipost, ChemoCentryx, Xalud
  - Business: Ambulomics Inc

- Y. Yazici, C.J. Swearingen, H. Ghandehari, J. Britt, I. Simsek, M. Fineman, S. Kennedy, J. Tambiah
  - Current or former employees of Biosplice Therapeutics, Inc.

- LOR is an investigational compound currently in clinical trials; LOR has not been approved by the FDA or any other pharmaceutical regulatory authority, and no conclusions can or should be drawn regarding the safety or effectiveness of the product candidate. The complete mechanism of action (MOA) for LOR is unknown, and further investigation is being conducted.
- This presentation is intended as a scientific exchange of medical information, is provided for educational purposes only, and is not intended for any promotional purpose or to offer medical advice.

Lorecivivint (LOR)

- LOR, a novel CLK/DYRK inhibitor thought to modulate Wnt and inflammatory pathways, is in development as a potential intra-articular (IA) knee OA treatment
- LOR appeared safe and demonstrated pain and function improvements compared with placebo in a Phase 2b randomized, controlled knee OA trial.[1]

1.Yazici Y, et al. *Osteoarthritis Cartilage.* 2017

STRIDES-X-ray (OA-11, NCT03928184) Study Design

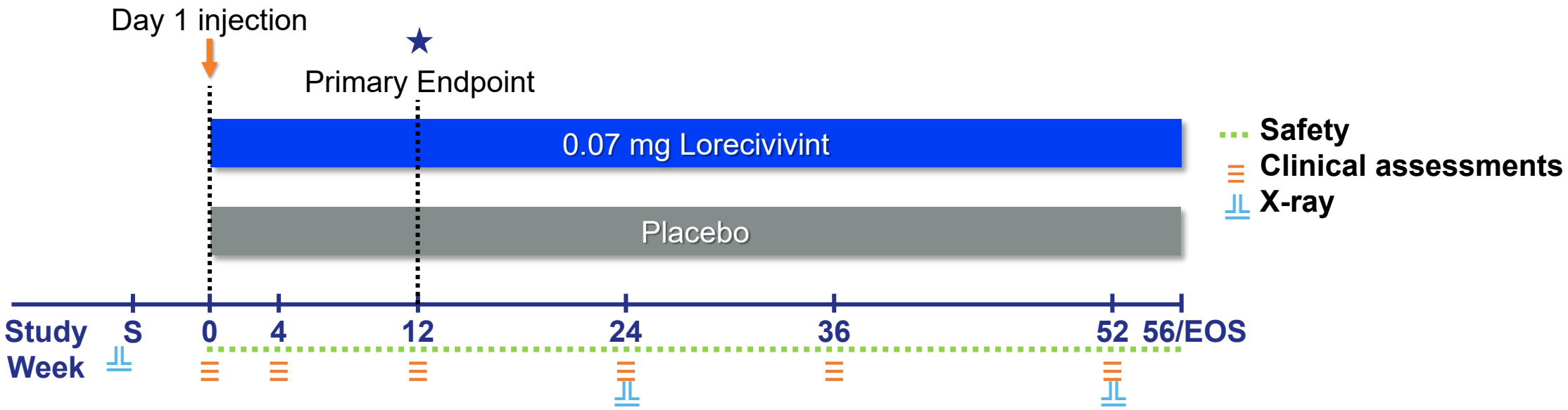
- Phase 3, 56-week RCT designed to test the safety and efficacy of 0.07 mg LOR in a population with structurally advanced knee OA to additionally evaluate effects on radiographic progression

– completing participants were able to enroll in a repeat injection extension study

- **Inclusion:** ACR-defined (clinical and radiographic) knee OA, Kellgren-Lawrence (KL) grades 2-3, baseline medial JSW 1.5-4.0 mm, and Pain NRS [0-10] ≥4 and ≤8 in the target knee and <4 in the contralateral knee

STRIDES-X-ray Study Design

Trial period 2019-2021



★ **Primary endpoint**

- Change from baseline in weekly average of daily pain NRS at Week 12

Other endpoints

- Change from baseline in medial JSW at Week 52 by positioned, fixed-flexion, P/A radiograph
- Change from baseline in Pain NRS, WOMAC Pain, and WOMAC Function at Week 52

NRS = Numeric rating scale, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; S = Screening, EOS = End of study

STRIDES-X-Ray Demographics

Full Analysis Set (FAS)	PBO	LOR 0.07 mg	All Subjects
N	253	248	501
Age - Years*	61.0 (± 8.7)	60.8 (± 8.0)	60.9 (± 8.3)
BMI - kg/m^2*	31.4 (± 4.83)	31.7 (± 4.55)	31.5 (± 4.69)
Female	163 (64.4%)	165 (66.5%)	328 (65.5%)
Race			
White	175 (69.2%)	171 (69.0%)	346 (69.1%)
African American	65 (25.7%)	66 (26.6%)	131 (26.1%)
Asian	7 (2.8%)	6 (2.4%)	13 (2.6%)
KL Grade 2	134 (53.0%)	124 (50.0%)	258 (51.5%)
Unilateral Symptomatic†	82 (32.4%)	80 (32.3%)	162 (32.3%)
Medial Joint Space Width (mm)	2.61 (± 0.69)	2.61 (± 0.74)	2.61 (± 0.72)

*Mean (± SD) reported. Otherwise, n (%) reported.
†Unilateral symptomatic as designated by principal investigator

Incidence of Adverse Events (AEs), Serious AEs, and Target-Knee AEs

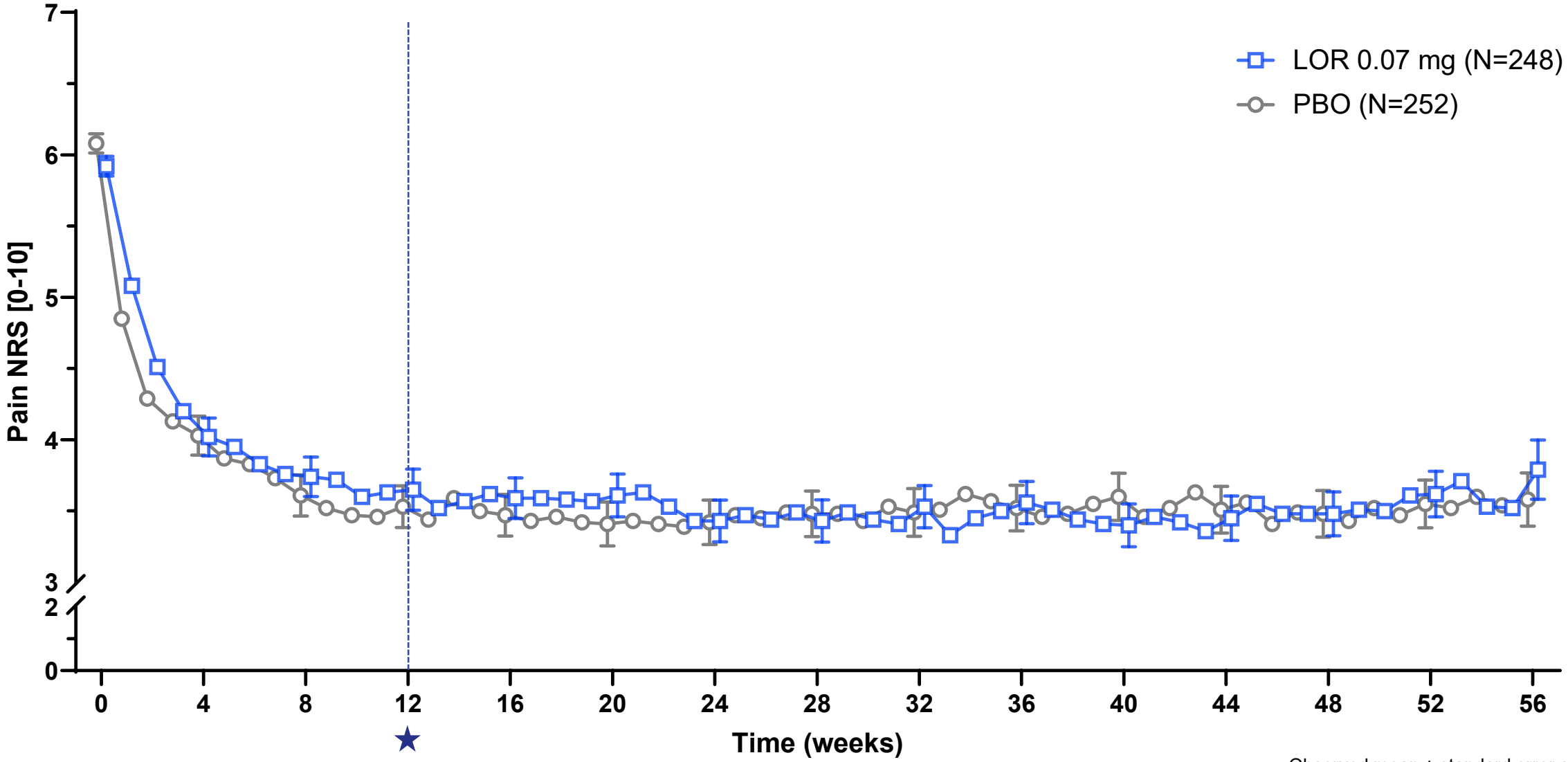
OA-11	Total Number (%) of Subjects	
	LOR N=249	PBO N=252
Adverse Events	136 (54.6%)	125 (49.6%)
SAEs*	12 (4.8%)	13 (5.2%)
Target-Knee AEs	18 (7.2%)	12 (4.8%)

*No SAEs deemed related to treatment by investigators

OA-11	AEs ≥ 2%	
Preferred Term N (%) subjects	**LOR N=249**	**PBO N=252**
Arthralgia	20 (8.0%)	17 (6.7%)
Urinary tract infection	16 (6.4%)	13 (5.2%)
Back pain	13 (5.2%)	8 (3.2%)
COVID-19	11 (4.4%)	7 (2.8%)
Joint swelling	7 (2.8%)	4 (1.6%)
Nasopharyngitis	7 (2.8%)	4 (1.6%)
Headache	6 (2.4%)	10 (4.0%)
Upper respiratory tract infection	6 (2.4%)	5 (2.0%)
Sciatica	6 (2.4%)	2 (0.8%)
Contusion	5 (2.0%)	5 (2.0%)
Osteoarthritis	5 (2.0%)	2 (0.8%)
Gastrooesophageal reflux disease	5 (2.0%)	1 (0.4%)
Sinusitis	4 (1.6%)	6 (2.4%)
Hypertension	3 (1.2%)	11 (4.4%)
Toothache	3 (1.2%)	5 (2.0%)
Bronchitis	2 (0.8%)	5 (2.0%)
Ligament sprain	2 (0.8%)	5 (2.0%)

STRIDES-X-Ray Weekly Average of Daily Pain NRS

Primary Endpoint (Full Analysis Set)

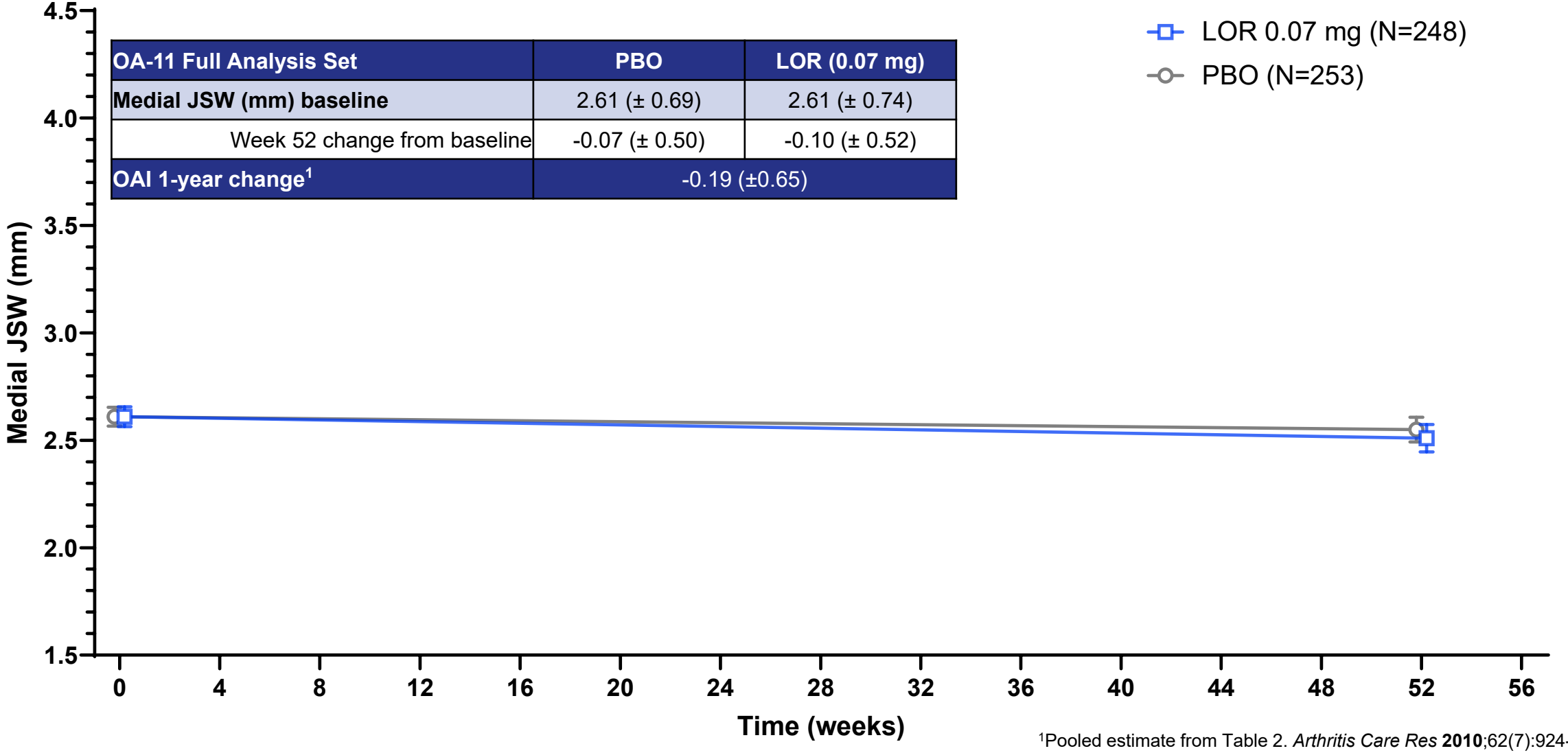


Observed mean ± standard error shown.

STRIDES-X-Ray Medial JSW

Other Endpoint (Full Analysis Set)

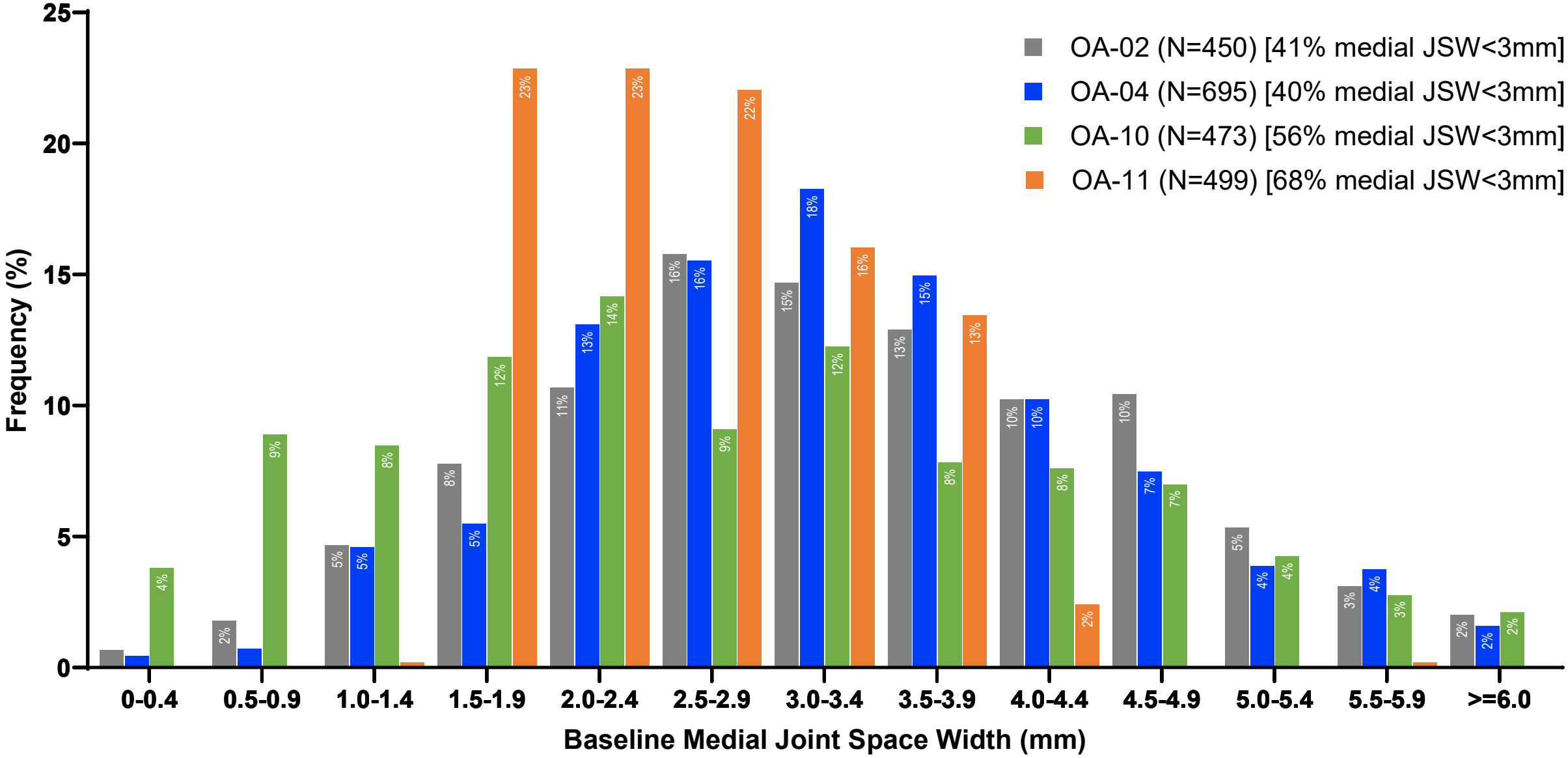
OA-11 Full Analysis Set	PBO	LOR (0.07 mg)
Medial JSW (mm) baseline	2.61 (± 0.69)	2.61 (± 0.74)
Week 52 change from baseline	-0.07 (± 0.50)	-0.10 (± 0.52)
OAI 1-year change[1]	-0.19 (±0.65)	



[1]Pooled estimate from Table 2. *Arthritis Care Res* **2010**;62(7):924-931.

Observed mean ± standard error shown 10

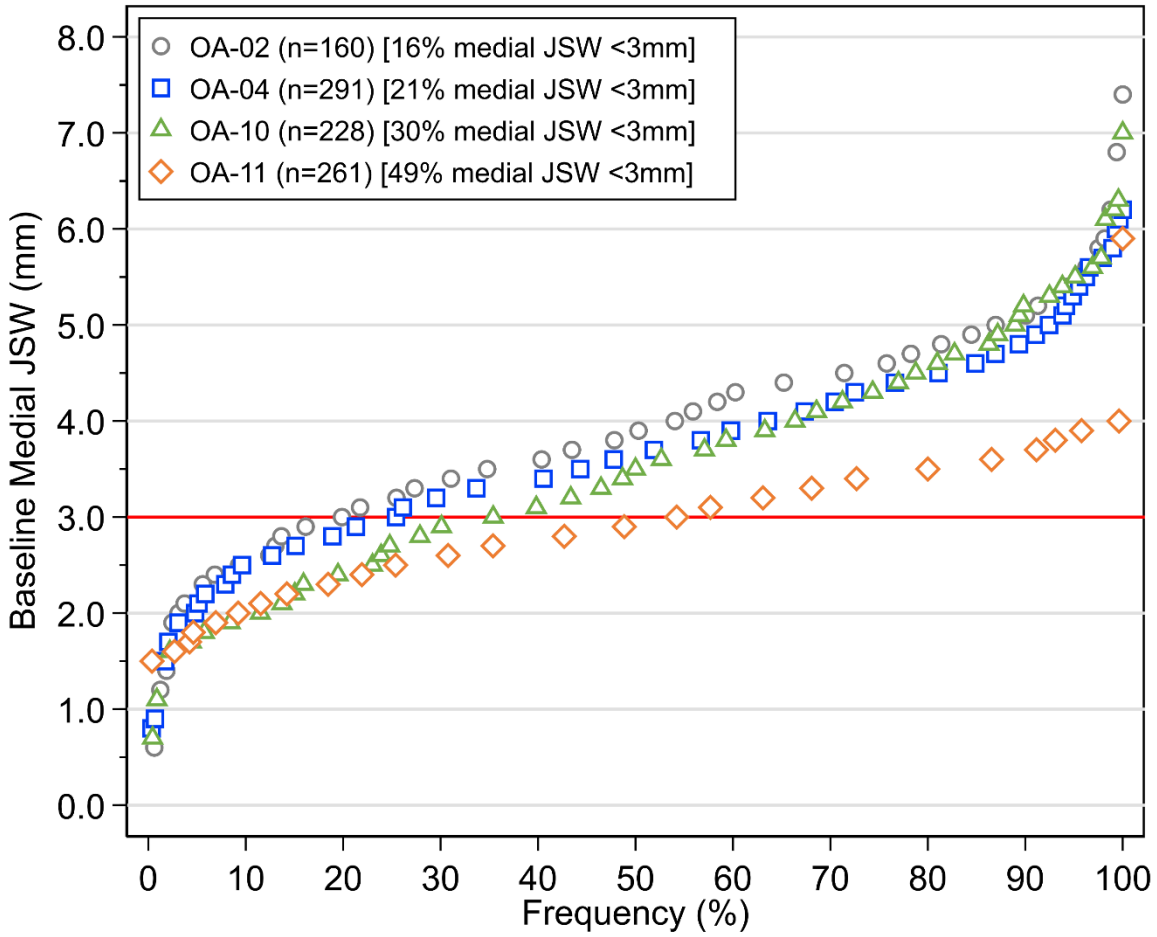
Distribution of Baseline medial JSW across Lorecivivint Studies



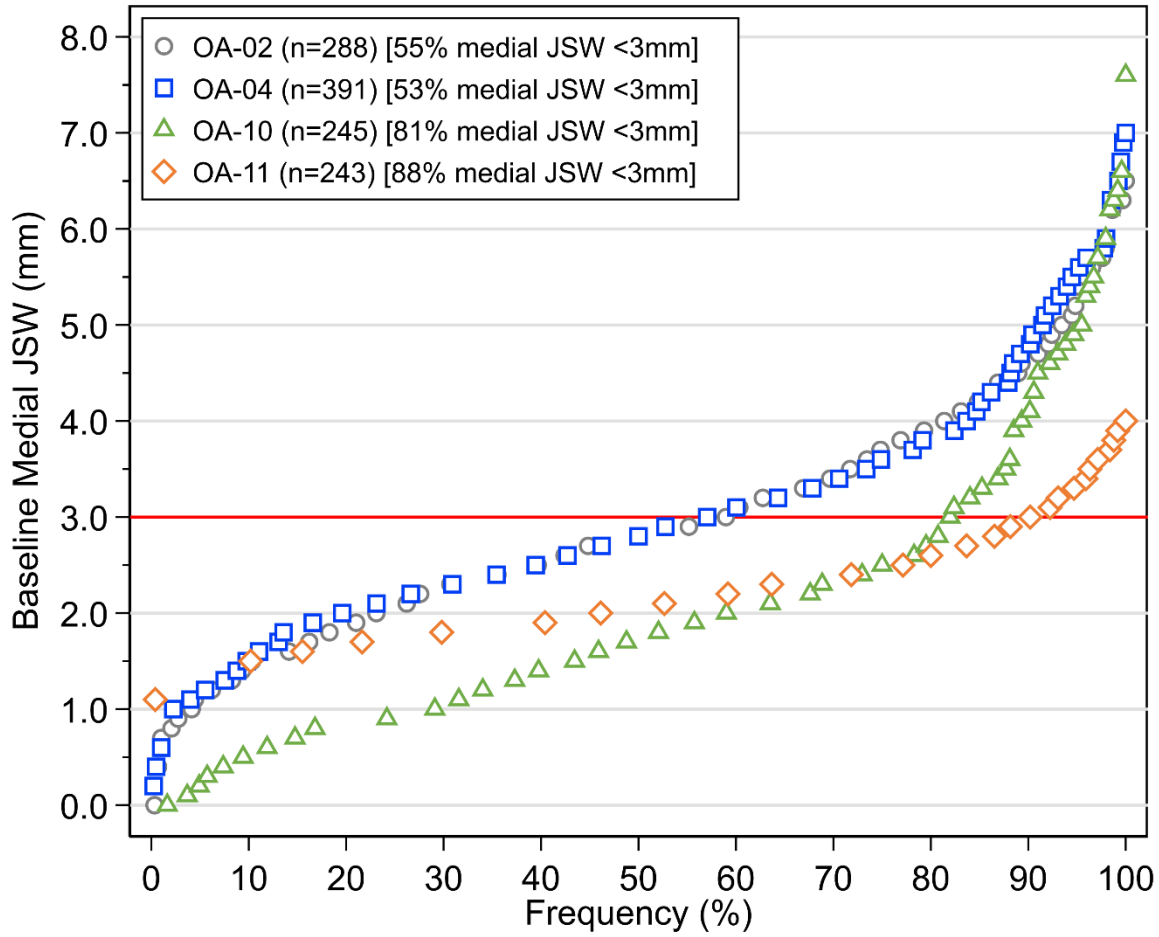
Baseline Medial JSW by KL Grade across LOR studies

Cumulative Distribution Plots

KL 2



KL 3



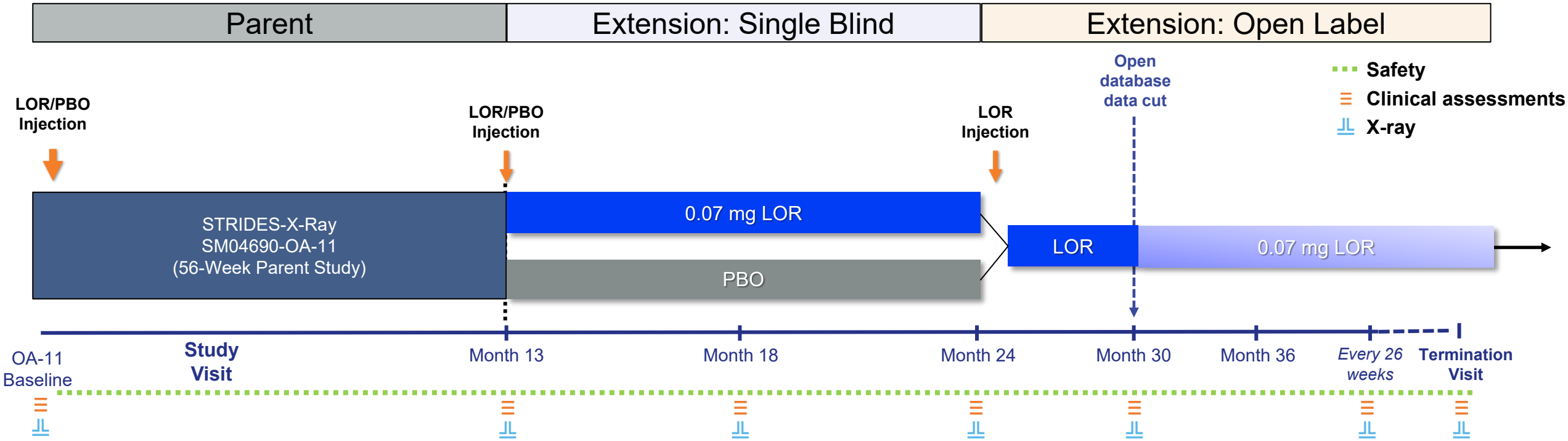
STRIDES X-Ray Conclusions

- LOR appeared safe and well tolerated
- LOR did not meet the primary endpoint of change from baseline in Pain NRS at week 12
- Participants in OA-11 had the most structurally advanced disease enrolled in the program to date, 68% baseline mJSW <3 mm
- Trial was conducted during COVID pandemic; effects on activity levels and pain PROs in knee OA patients have been reported[1,2]

- Completing participants were able to enroll in OA-07 extension trial

1. Larghi et al., *Acta Biomed* 2020
2. Endstrasser et al., *ESSKA* 2020

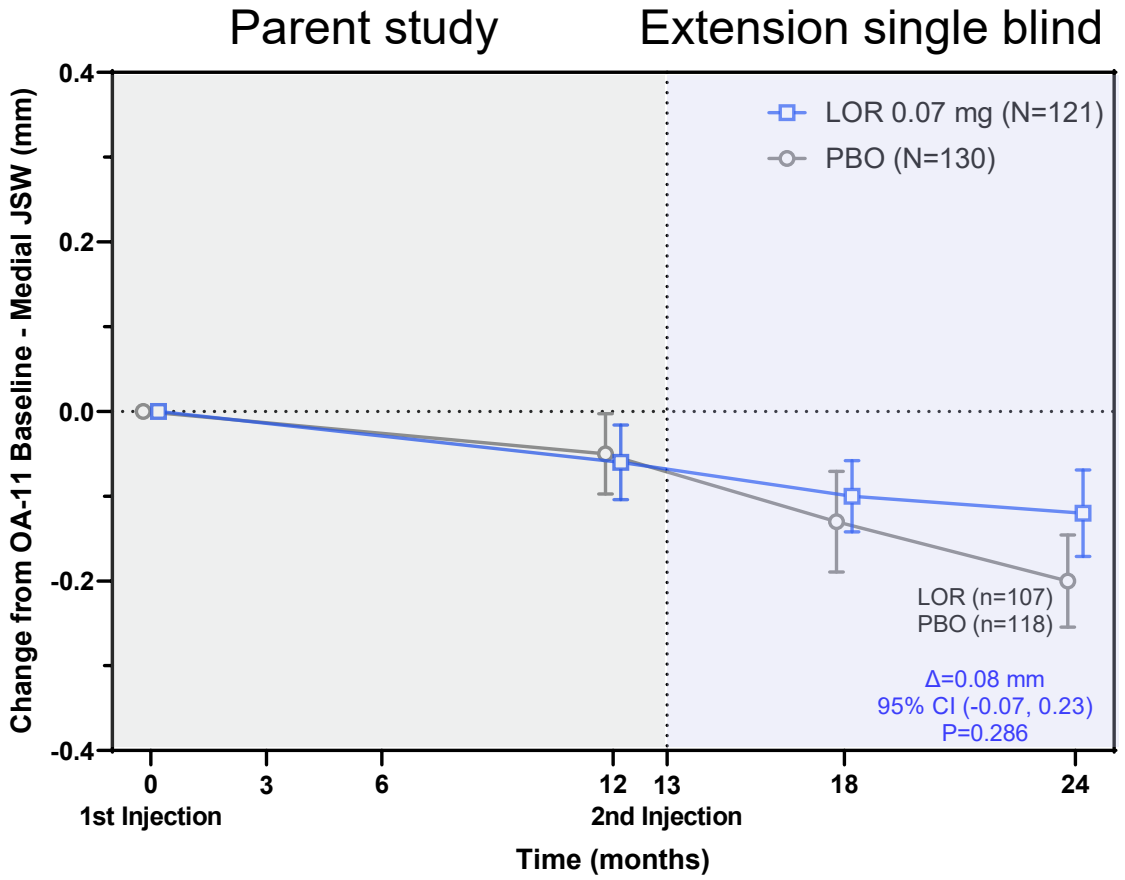
STRIDES X-Ray Extension: Study Design



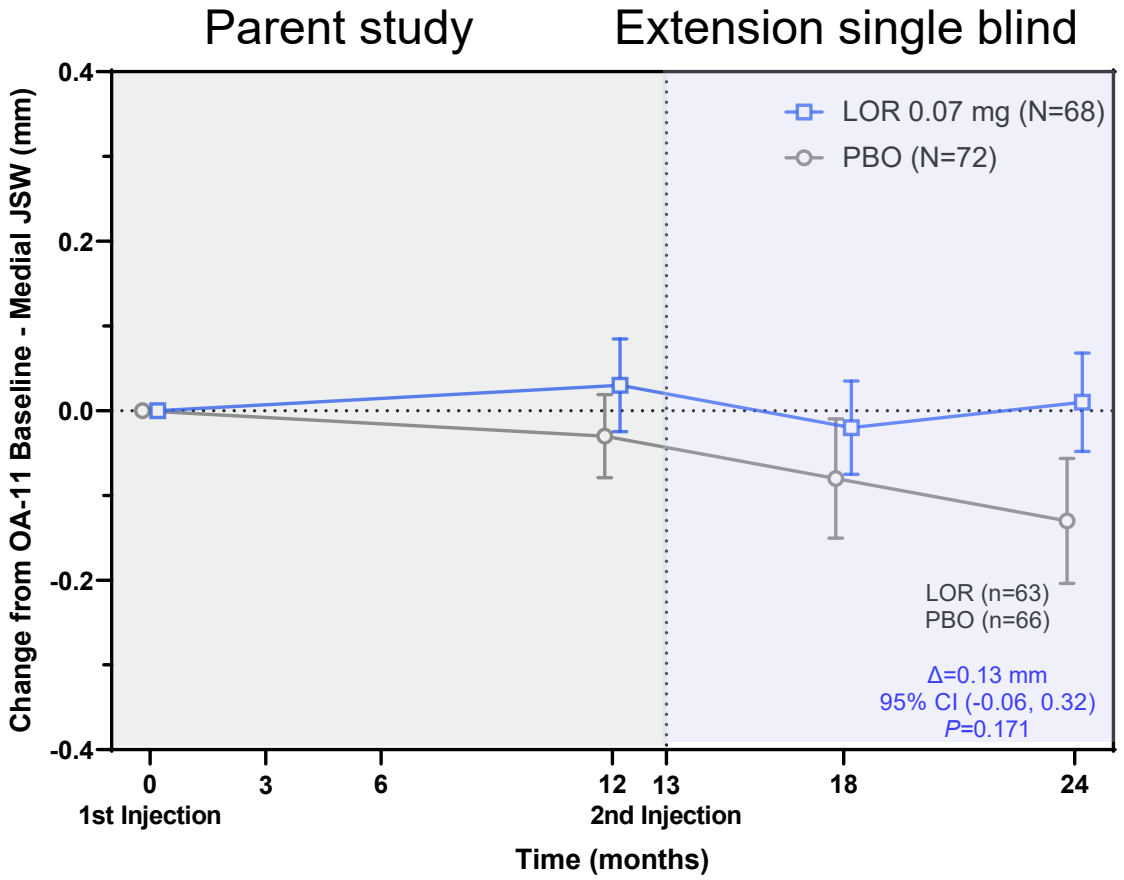
- ~50% of pts joined the extension study
- **Participant characteristics were similar between studies**
- **Participants and investigators remained blind to initial treatment throughout.**

Extension study: change in medial JSW

Extension Study All Subjects



KL 2 Subset



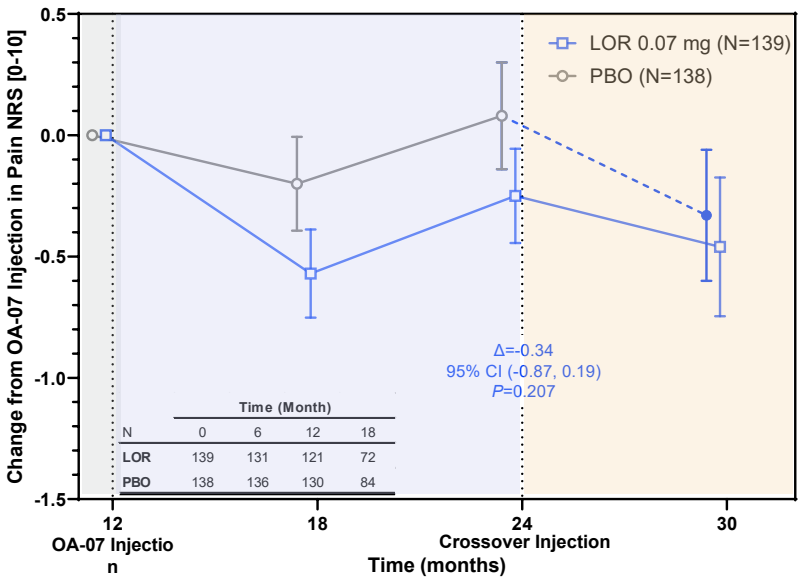
Observed mean ± standard error shown. Data from open database.
*P-value reported from OA-11 baseline-adjusted ANCOVA at timepoint.

Extension Study: Change in PROs from Extension Baseline

FAS

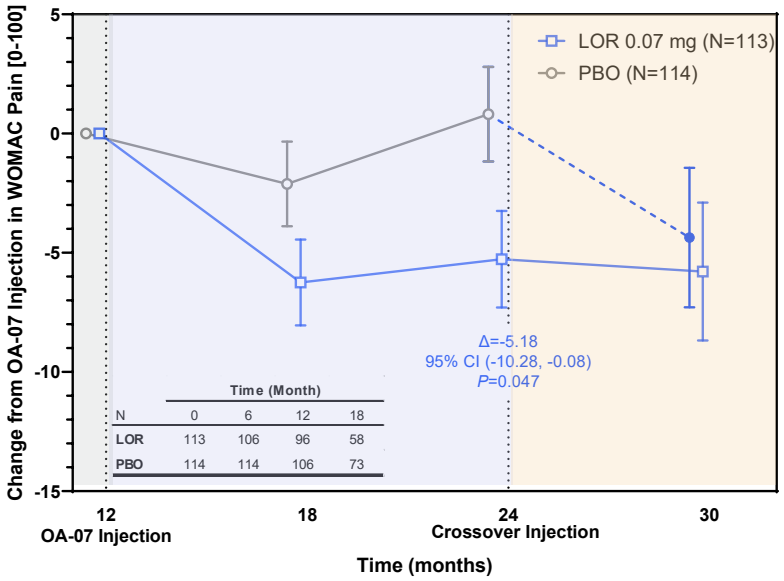
Pain NRS

Single Blind Open Label



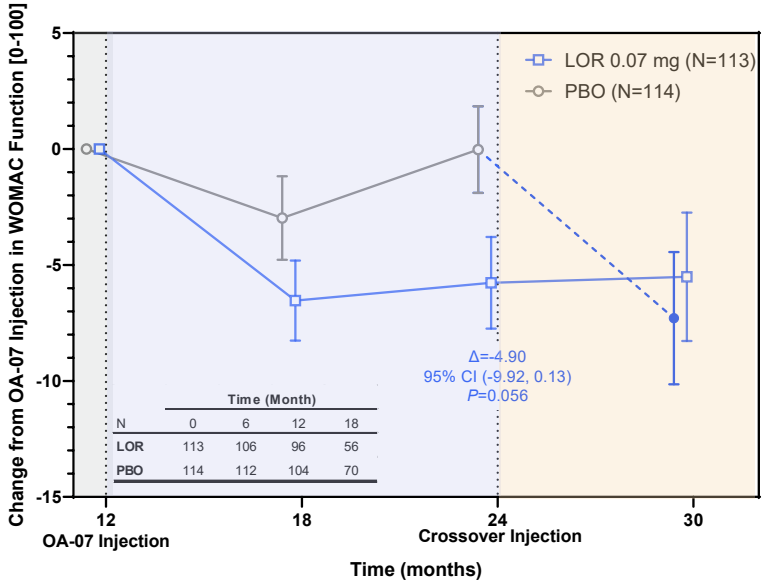
WOMAC Pain

Single Blind Open Label



WOMAC Function

Single Blind Open Label



Observed mean ± standard error shown. Data from open database.
**P*-value reported from OA-07 baseline-adjusted ANCOVA at timepoint.

Extension study conclusions

- LOR safety profile remains comparable to PBO
- Data from this ongoing trial suggest signals of potential benefit of LOR 0.07 mg compared with PBO 12 months after OA-07 injection:
  - Pain NRS, WOMAC Function, and WOMAC Pain FAS
  - Medial JSW, especially for KL 2 participants
- PBO medial JSW progression in OA-07 single blind compared to OA-11 suggests potential pandemic impact on trial
- PBO participant PRO responses observed after crossover LOR injection are suggestive of drug effect

Final conclusions

- Strides-X-Ray parent trial did not meet its primary endpoint
  - Enrolled the most structurally advanced knee OA participants in LOR program
  - Was largely conducted during the COVID-19 pandemic
- Preliminary analysis of the extension trial shows potential for structural and symptomatic efficacy following second LOR injection
- Greater structural benefit signal in KL 2 supports earlier LOR intervention
- Additional trial of LOR in participants with moderate to severe pain of knee OA with less advanced structural disease (STRIDES, OA-21) is planned to start in 2022

Thank you

Biosplice thanks the investigators and participants for their time and effort necessary for this trial.