Radiographic and Pain Outcomes from a Phase 3 Extension Study Evaluating the Safety and Efficacy of Lorecivivint in Subjects with Severe Osteoarthritis of the Knee (OA-07): 36 Month Single Blind and Placebo Crossover Phase Results

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Disclosures

- Y. Yazici
  - Chief Medical Officer, Biosplice Therapeutics, Inc.

- C.J. Swearingen, J. Tambiah
  - Current or former employees of Biosplice Therapeutics, Inc.

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

- Lorecivivint is an investigational compound currently in clinical trials; lorecivivint 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 for lorecivivint 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.

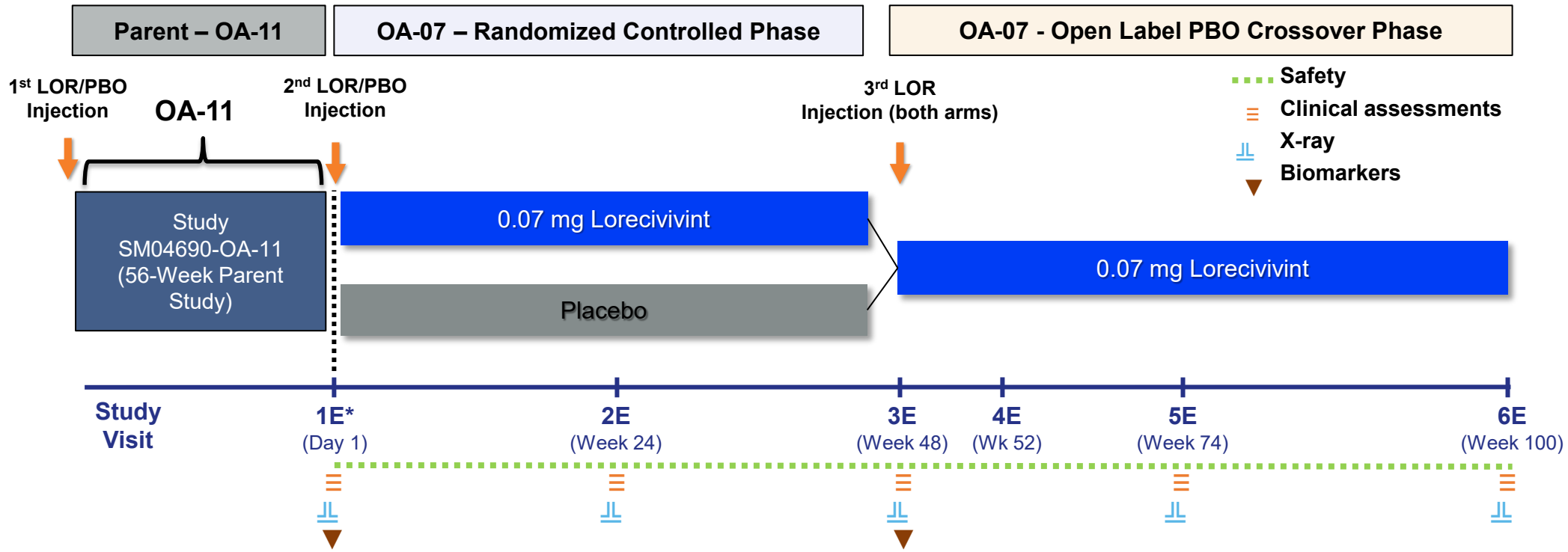
Background

- **Lorecivivint (LOR)** - CLK/DYRK inhibitor thought to modulate inflammatory/Wnt pathways, in development as IA knee OA treatment

- Objective of OA-07 study was to evaluate efficacy and safety of repeat IA 0.07 mg LOR using patient reported outcomes (WOMAC Pain, WOMAC Function) and radiographic medial joint space width (JSW)

1. Yazici Y, et al. *OAC* 2017
2. Larghi et al., *Acta Biomed* 2020
3. Endstrasser et al., *ESSKA* 2020

Methods: OA-07 Trial Design



- Primary Efficacy Objective: Change from baseline in target knee medial joint space width
- ~50% of OA-11 patients enrolled into the OA-07 trial
- Patient characteristics similar between OA-11 and OA-07 trial
- Patients and investigators remained blinded to initial treatment throughout

Demographics: Summary by Enrollment into OA-07

	OA-11		Not Enrolled OA-07		OA-07	
	PBO	LOR	PBO	LOR	PBO	LOR
N	253	248	115	110	138	138
Age (years)*	61.0 (8.7)	60.8 (8.0)	60.4 (8.7)	61.2 (8.3)	61.6 (8.6)	60.5 (7.7)
Female [N (%)]	163 (64.4%)	165 (66.5%)	80 (69.6%)	75 (68.2%)	83 (60.1%)	90 (65.2%)
Race [N (%)]						
White	175 (69.2%)	171 (69.0%)	79 (68.7%)	71 (64.5%)	96 (69.6%)	100 (72.5%)
Black	65 (25.7%)	66 (26.6%)	30 (26.1%)	30 (27.3%)	35 (25.4%)	36 (26.1%)
Other	13 (5.1%)	11 (4.4%)	6 (5.2%)	9 (8.2%)	7 (5.0%)	2 (1.4%)
Hispanic / Latino [N (%)]	54 (21.3%)	46 (18.5%)	24 (20.9%)	24 (21.8%)	30 (21.7%)	22 (15.9%)
KL Grade 2 [N (%)]	134 (53.0%)	124 (50.0%)	57 (49.6%)	50 (45.5%)	77 (55.8%)	74 (53.6%)
Unilateral Symptomatic OA [N (%)]	82 (32.4%)	80 (32.3%)	42 (36.5%)	30 (27.3%)	40 (29.0%)	50 (36.2%)
BMI (kg/m^2)*	31.41 (4.83)	31.66 (4.55)	30.96 (4.85)	31.40 (4.03)	31.79 (4.80)	31.87 (4.93)

*Mean (SD) reported. Otherwise, N (%) reported.

OA-11 Outcomes Summary by Enrollment into OA-07

	OA-11		Not Enrolled OA-07		OA-07	
	PBO	LOR	PBO	LOR	PBO	LOR
Pain NRS [0-10]						
Baseline	6.08 (1.08)	5.92 (1.09)	6.02 (1.24)	5.98 (1.16)	6.13 (0.92)	5.87 (1.03)
WOMAC Pain [0-100]						
Baseline	59.06 (10.73)	56.83 (10.18)	58.30 (11.53)	56.70 (10.31)	59.68 (10.02)	56.93 (10.11)
WOMAC Function [0-100]						
Baseline	59.54 (10.25)	59.08 (10.13)	59.82 (10.48)	58.89 (10.13)	59.32 (10.09)	59.23 (10.17)
Medial JSW (mm)						
Baseline	2.61 (0.69)	2.61 (0.74)	2.57 (0.77)	2.59 (0.74)	2.64 (0.63)	2.62 (0.75)

*Mean (SD) reported.

OA-11 Safety Summary by Enrollment into OA-07

	OA-11		Not Enrolled OA-07		OA-07	
	PBO	LOR	PBO	LOR	PBO	LOR
N	253	248	115	110	138	138
Any Adverse Event	125 (49.4%)	136 (54.6%)	63 (54.8%)	64 (58.2%)	62 (44.9%)	72 (52.2%)
Any Serious Adverse Event	13 (5.1%)	12 (4.8%)	4 (3.5%)	5 (4.5%)	9 (6.5%)	7 (5.1%)
Any Target Knee Adverse Event	12 (4.7%)	18 (7.3%)	5 (4.3%)	9 (8.2%)	7 (5.1%)	9 (6.5%)

Number of subjects (%) reporting at least one adverse event reported.

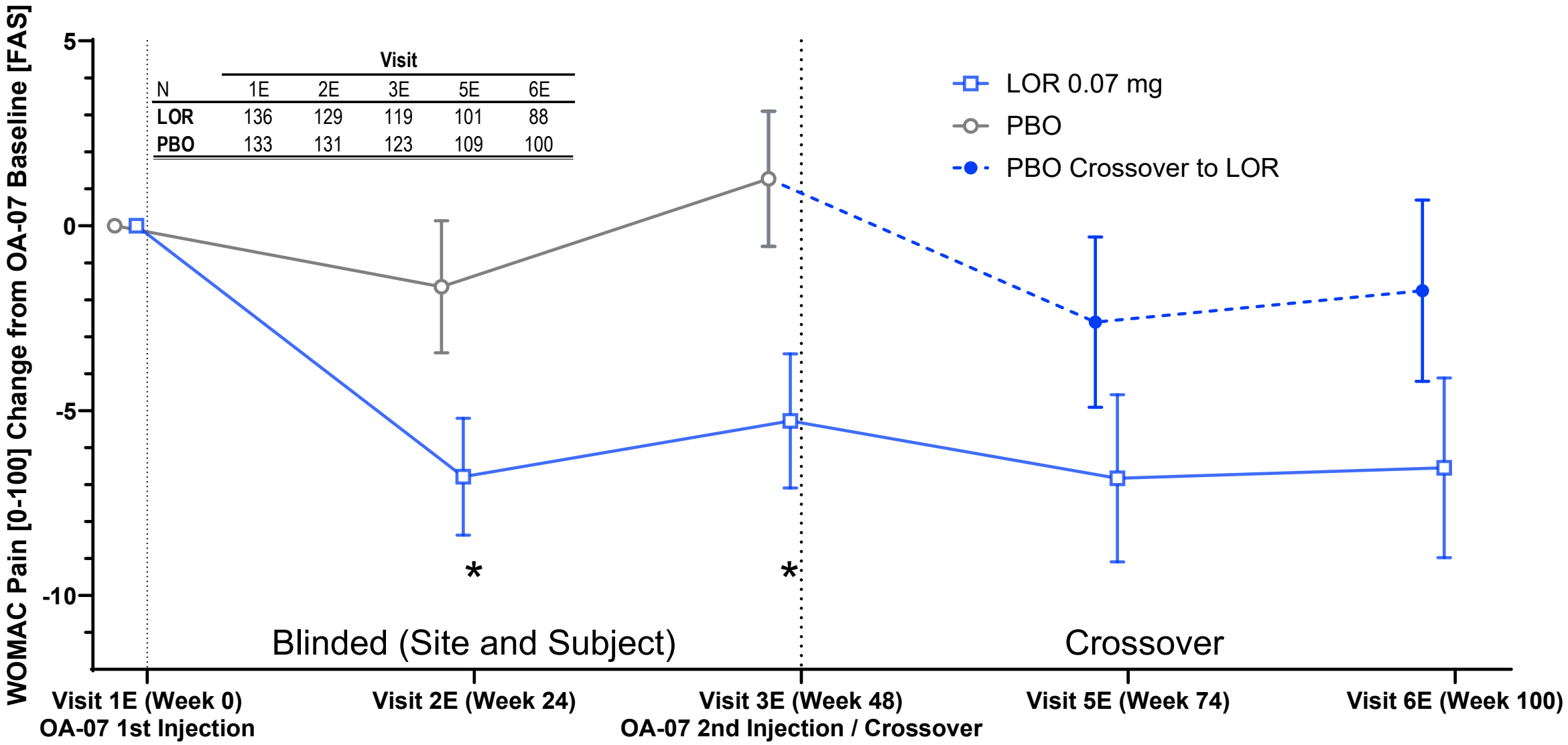
Results: OA-07 Adverse Events Overview

By Actual Treatment at Study Start

	Year 1		Crossover Year 1		Crossover Year 2	
	PBO	**LOR**	**PBO-LOR**	**LOR**	**PBO-LOR**	**LOR**
N	138	138	118	110	99	85
Total # of AEs	83	76	38	58	23	12
Subjects (%) Reporting at Least One AE:	44 (31.9%)	45 (32.6%)	28 (23.7%)	36 (32.7%)	12 (12.1%)	9 (10.6%)
Serious	4 (2.9%)	2 (1.4%)	3 (2.5%)	4 (3.6%)	3 (3.0%)	1 (1.2%)
Not Serious	40 (29.0%)	43 (31.2%)	25 (21.2%)	32 (29.1%)	9 (9.1%)	8 (9.4%)
Knee AEs						
Target	3 (2.2%)	2 (1.4%)	0 (0.0%)	2 (1.8%)	2 (2.0%)	0 (0.0%)
Non-Target	3 (2.2%)	1 (0.7%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	1 (1.2%)
AE Leading To:						
Discontinuation of Study Drug	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Withdrawal from the Study	1 (0.7%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (1.2%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)

*Only one AE in OA-07 was considered related by Investigator (PBO)

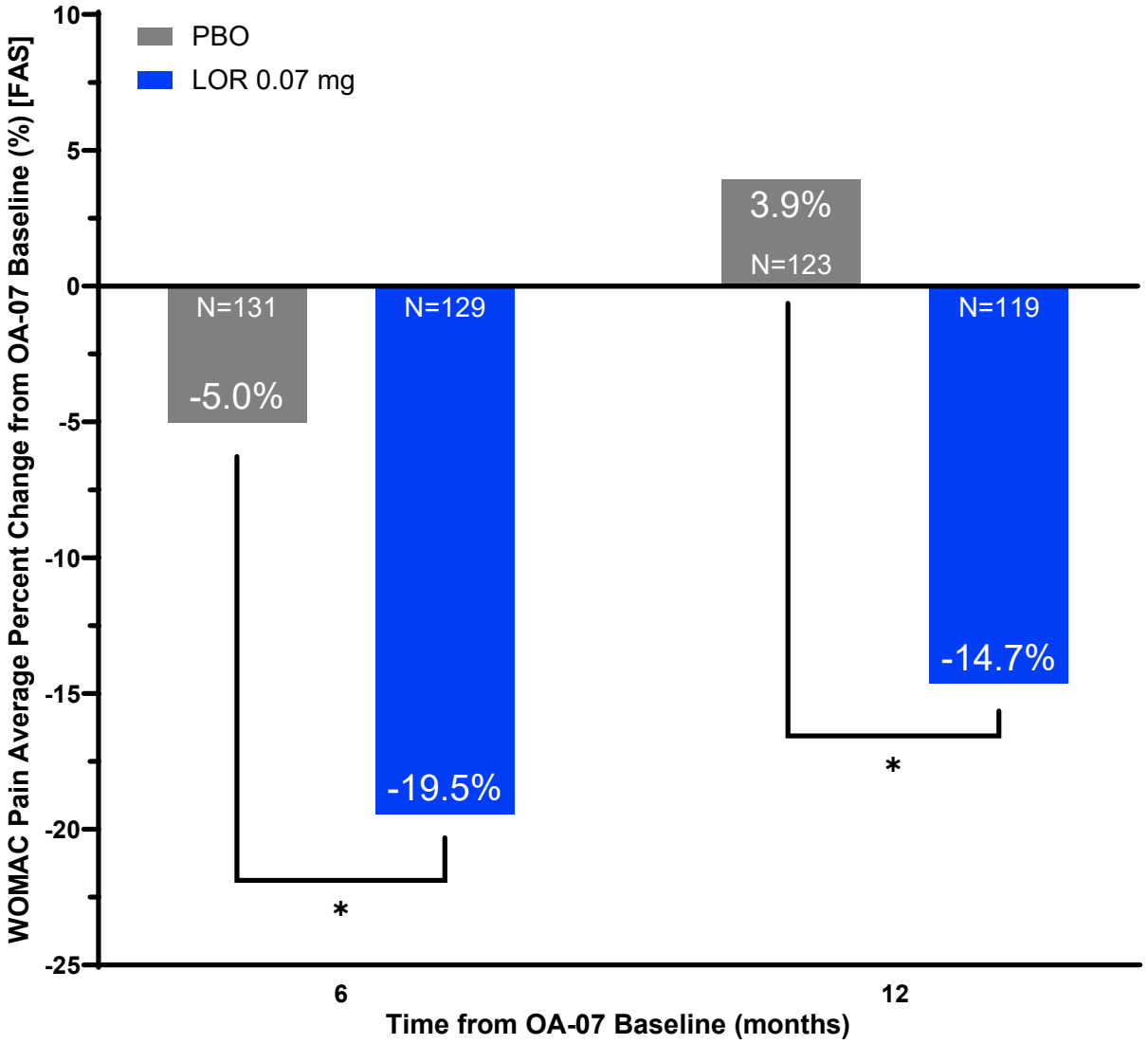
Results: WOMAC Pain



Observed mean ± standard error shown.
*P<0.05 LOR 0.07mg vs PBO from OA-07 baseline-adjusted ANCOVA

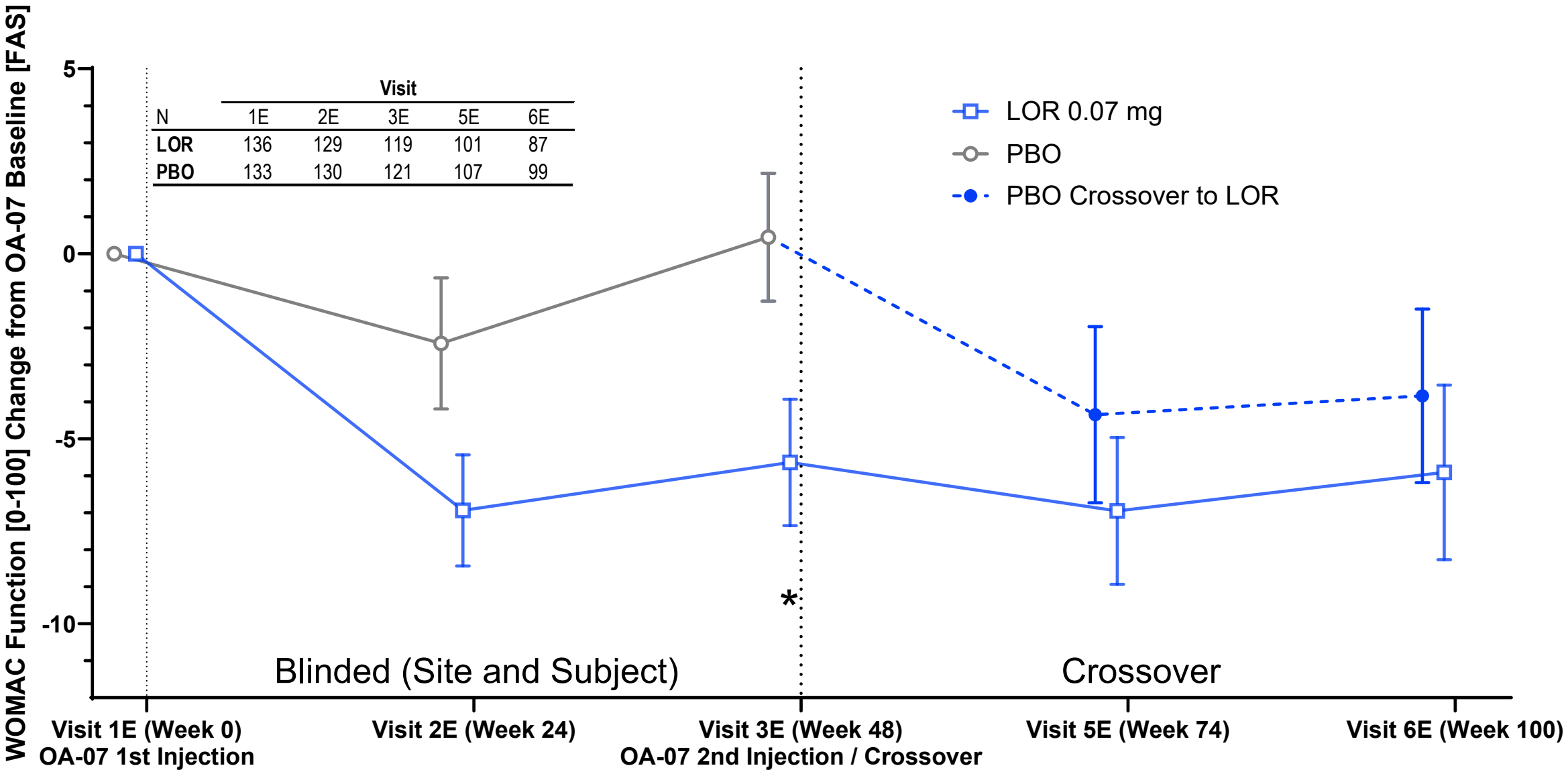
FAS=Full Analysis set; **WOMAC**=Western Ontario & McMaster Universities Arthritis Index; **LOR**=lorecivivint; **PBO**=placebo

WOMAC Pain Change from Baseline (%)



Observed mean change repreesented as percent change shown.
*P<0.05 LOR 0.07mg vs PBO from OA-07 baseline-adjusted ANCOVA

Results: WOMAC Function



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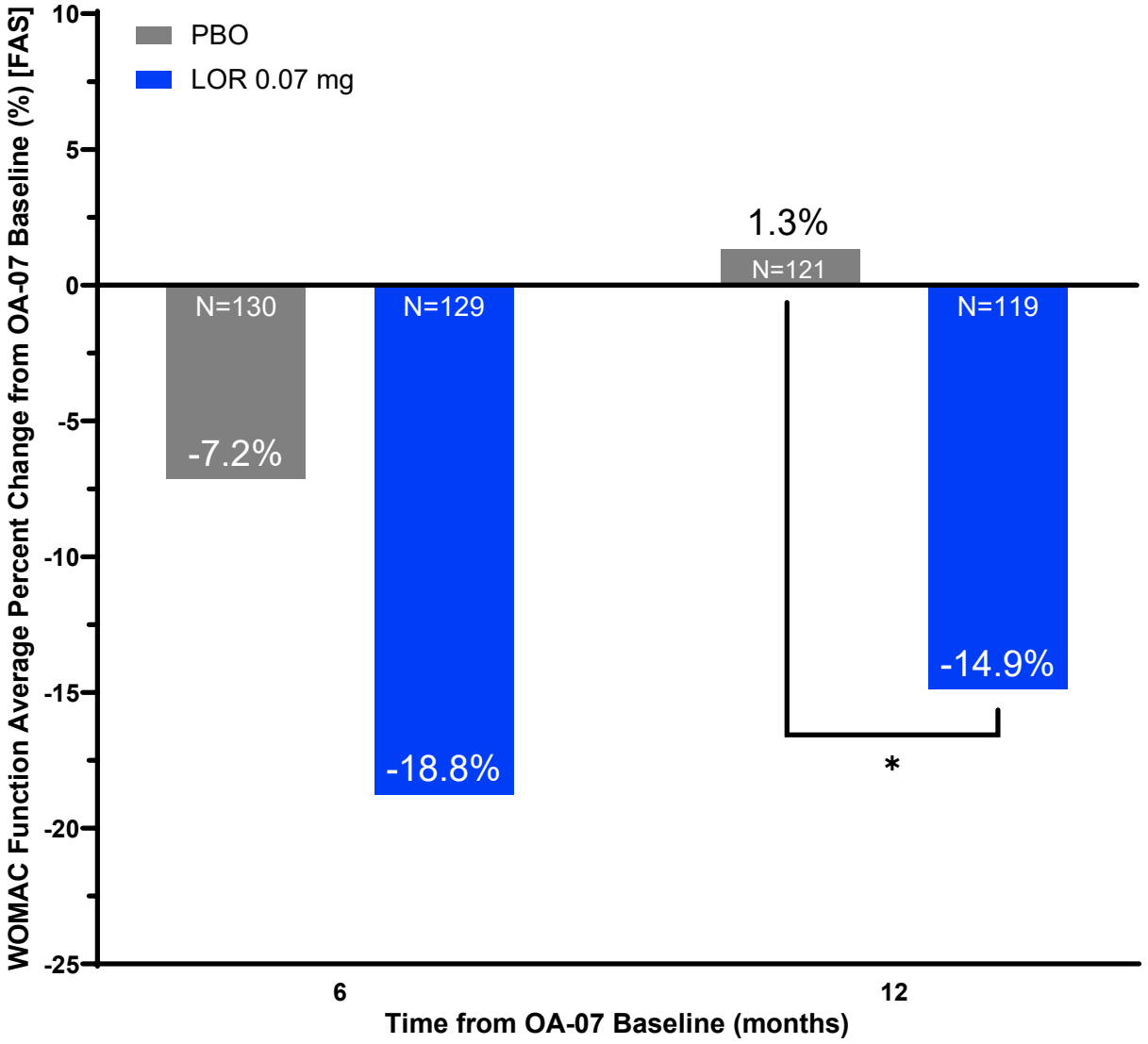
WOMAC Function Change from Baseline (%)



Observed mean change repreesented as percent change shown.
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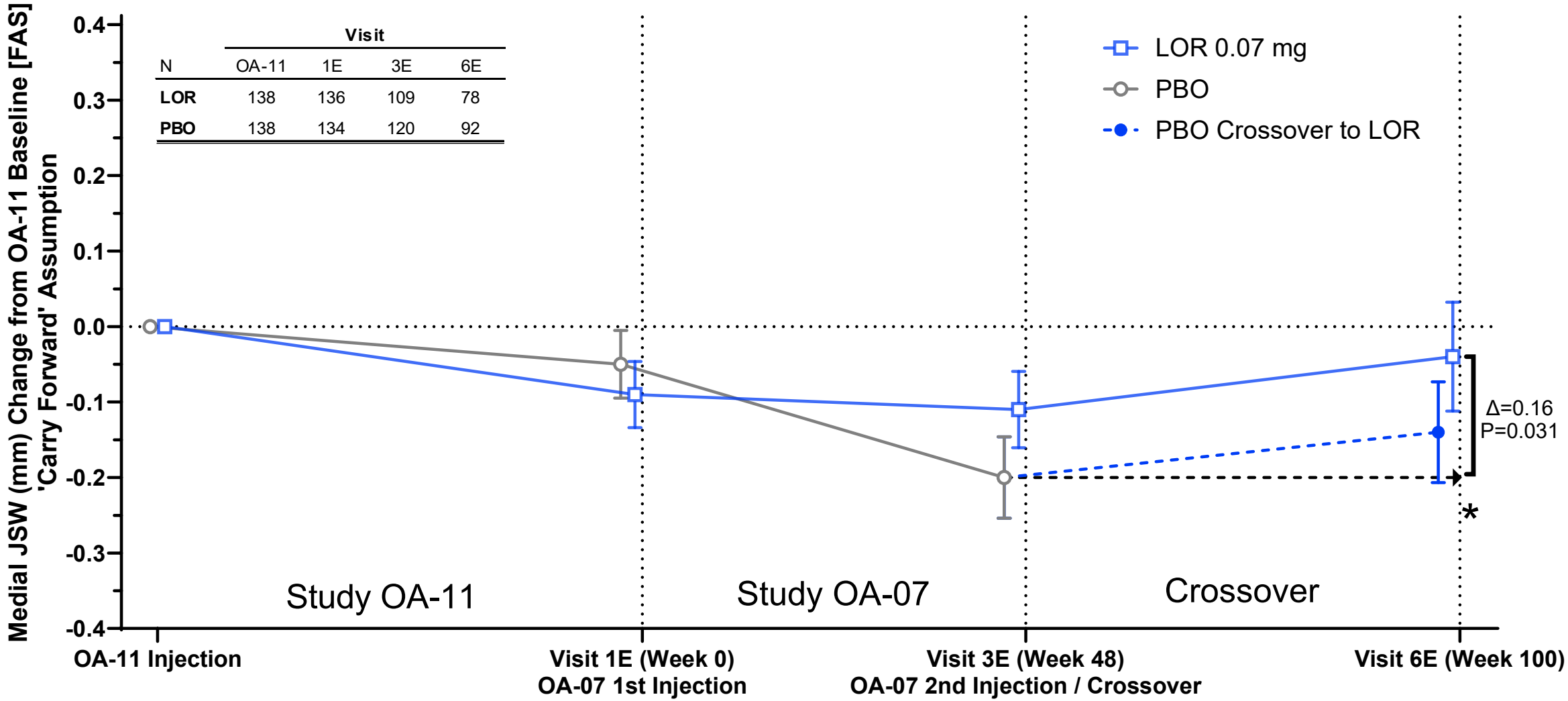
Results: Structural Improvement FAS



	Visit			
N	OA-11	1E	3E	6E
LOR	138	136	109	78
PBO	138	134	120	92

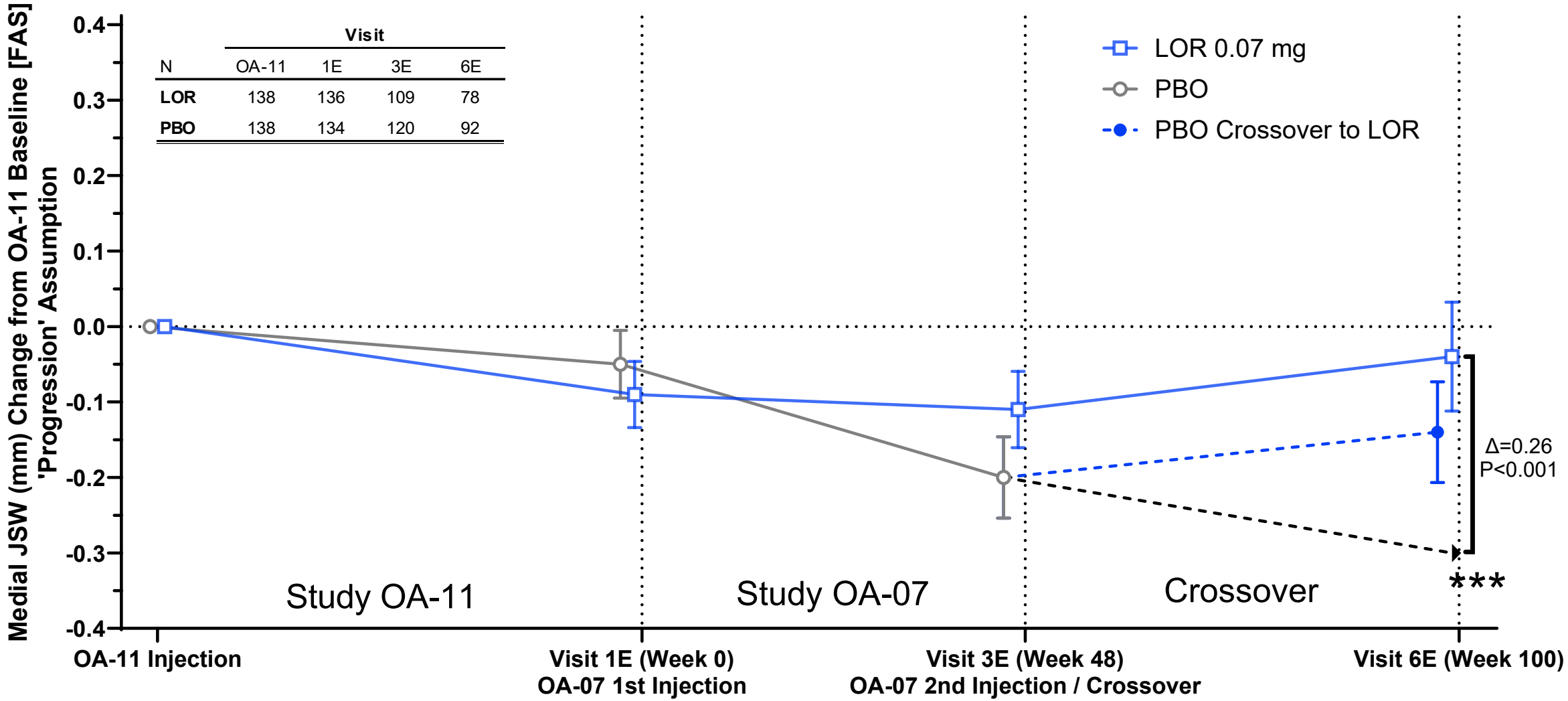
Observed mean ± standard error shown.

*P<0.05 LOR 0.07mg baseline-adjusted ANCOVA estimate tested against the PBO assumption.

0.13 mm represents actual or true change on x-ray. *Osteoarthritis Cartilage*. 2003;11:716-24

FAS=Full Analysis set; **JSW**=Joint Space Width; **mm**=millimeter; **LOR**=lorecivivint; **PBO**=placebo

Results: Structural Improvement FAS



Observed mean ± standard error shown.

0.13 mm represents actual or true change on x-ray. *Osteoarthritis Cartilage*. 2003;11:716-24

***P<0.001 LOR 0.07mg baseline-adjusted ANCOVA estimate tested against the PBO assumption.

FAS=Full Analysis set; **JSW**=Joint Space Width; **mm**=millimeter; **LOR**=lorecivivint; **PBO**=placebo

Conclusions

In this advanced knee OA cohort:

- Repeat LOR injections met the objectives of demonstrating efficacy and safety
  - Pain and function were both improved at 6 and 12 months compared to PBO
  - Structure was improved at 36 months compared to PBO imputations
  - PBO patients crossing over to LOR also showed PRO and structure improvements, reinforcing potential treatment effects
- LOR appeared safe and well-tolerated, consistent with previous trials

LOR has the potential to be the first DMOAD for the treatment of knee OA

Thank you