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
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- C.J. Swearingen, Lopez V, J. Britt, S. Kennedy, 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.

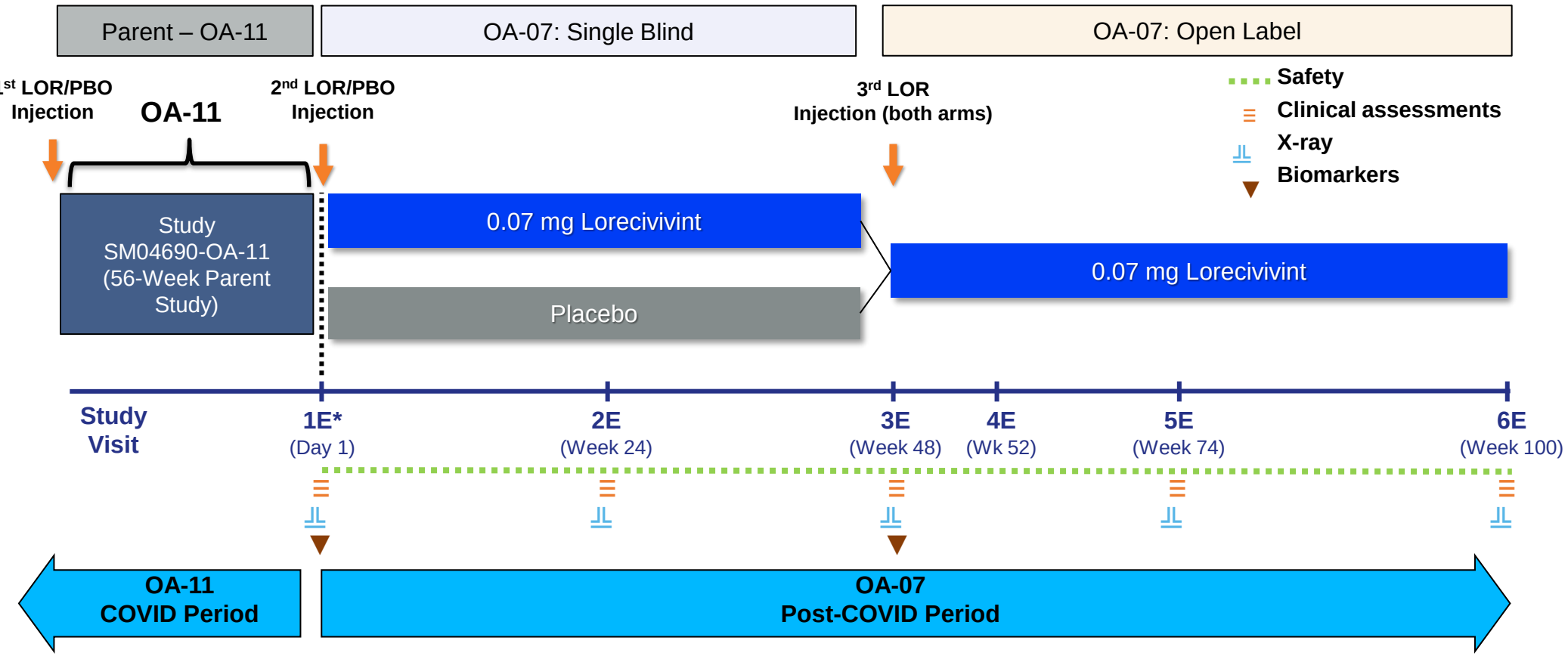
- Lorecivivint is an investigational compound currently in clinical trials; lorecivivint has not been approved by the FDA or any other pharmaceutical regulatory authority, and no conclusions can or should be drawn regarding the safety or effectiveness of the product candidate. The complete mechanism 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.

Lorecivivint (LOR)

- A novel CLK/DYRK inhibitor thought to modulate Wnt / inflammatory pathways, in development as an IA knee OA treatment.
- Demonstrated pain, function and structural improvements compared with placebo (PBO) in phase 2[1]
- Phase 3 trials, OA-10/11 did not meet primary endpoints. Potential factors:
  - OA-10 /11 had more severe baseline structural knee OA vs phase 2 trials
  - Pandemic environment likely affected pain / function reporting[2,3], lack of OA progression
  - OA-10 KL2 sub-population showed LOR symptomatic treatment effects
- The safety and efficacy of repeat IA 0.07 mg LOR was evaluated in the OA-07 trial, a 2- year extension of the OA-11 trial, in patients with structurally advanced knee OA to evaluate effects on radiographic medial joint space width (JSW) and patient reported outcomes (PRO)

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

OA-07 Trial Design



- Primary Efficacy Objective: Change from baseline in target knee medial joint space width
- ~50% of participants enrolled into the extension trial
- Participant characteristics were similar between parent and extension trial
- Participants and investigators remained blinded to initial treatment throughout

OA-07 Demographics

	PBO	LOR
N	138	138
Age (years)*	61.6 (8.6)	60.5 (7.7)
Female [N (%)]	83 (60.1%)	90 (65.2%)
Race [N (%)]		
White	96 (69.6%)	100 (72.5%)
Black	35 (25.4%)	36 (26.1%)
Other	7 (5.0%)	2 (1.4%)
Hispanic / Latino [N (%)]	30 (21.7%)	22 (15.9%)
KL Grade 2 [N (%)]	77 (55.8%)	74 (53.6%)
Unilateral Symptomatic OA [N (%)]	40 (29.0%)	50 (36.2%)
BMI (kg/m^2)*	31.79 (4.80)	31.87 (4.93)

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

OA-07 Adverse Events Overview

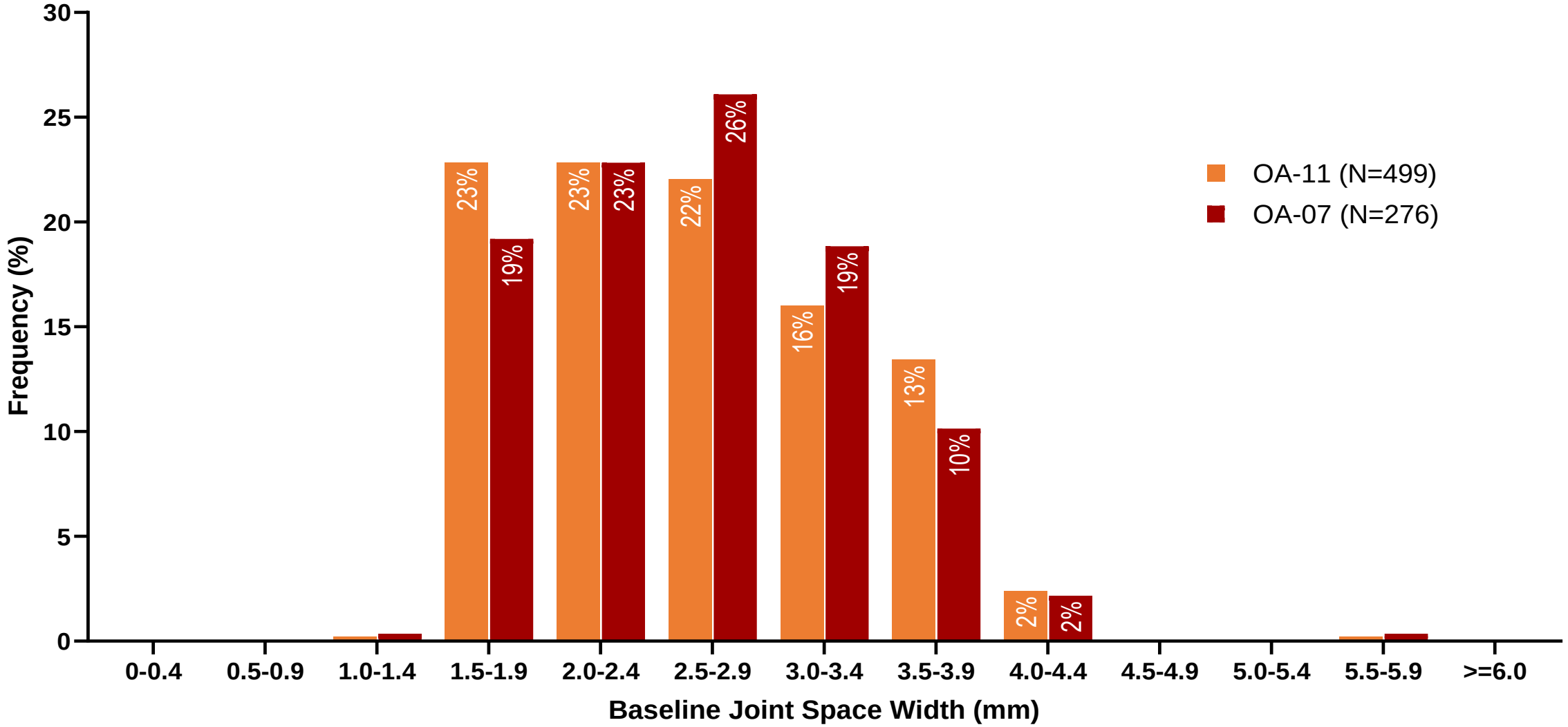
By Actual Treatment at Study Start

	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%)

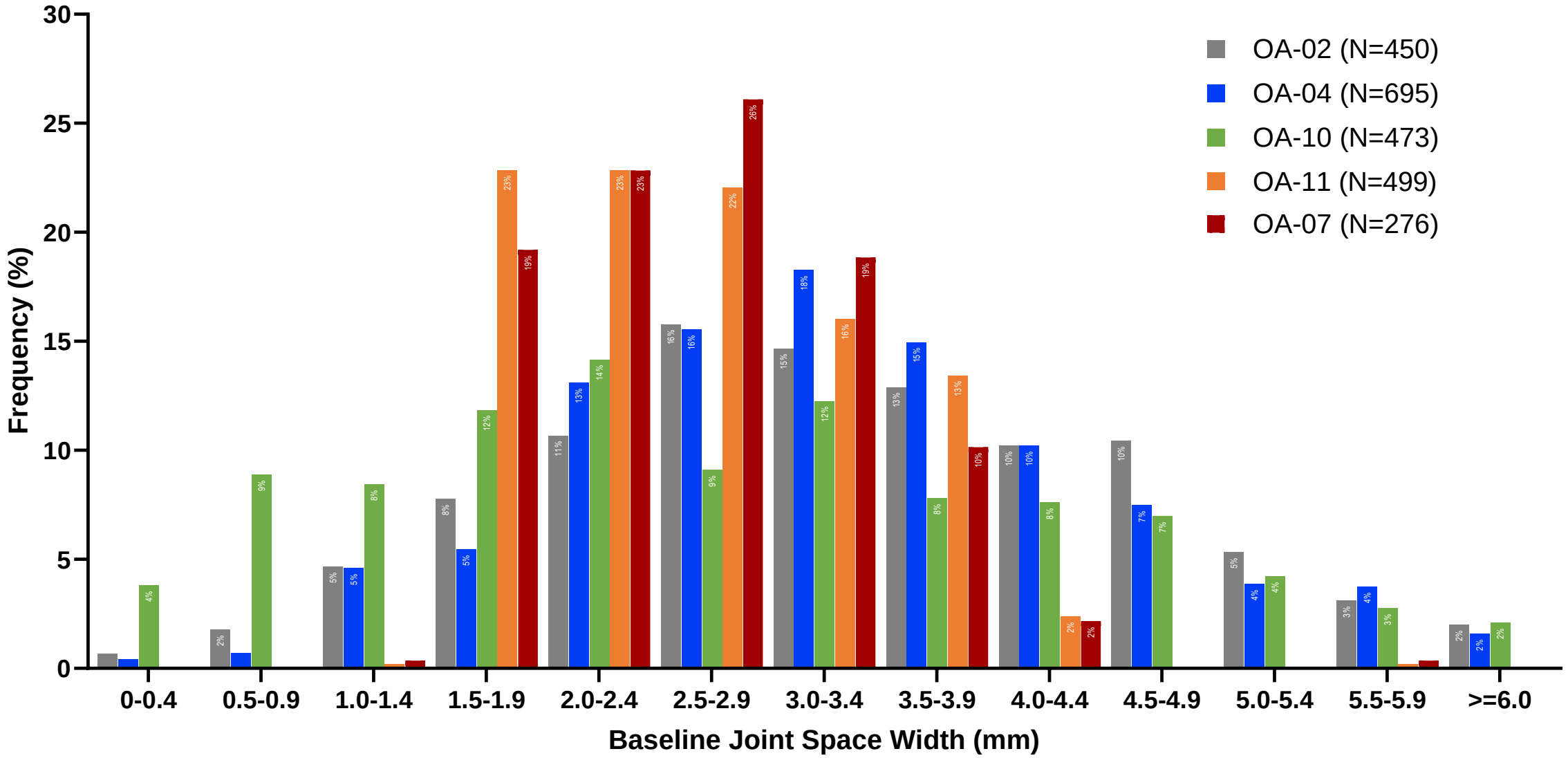
*Only one AE in OA-07 was considered related by Investigator (PBO)

Draft analysis from a closed database.

Baseline medial JSW for OA-11 and OA-07

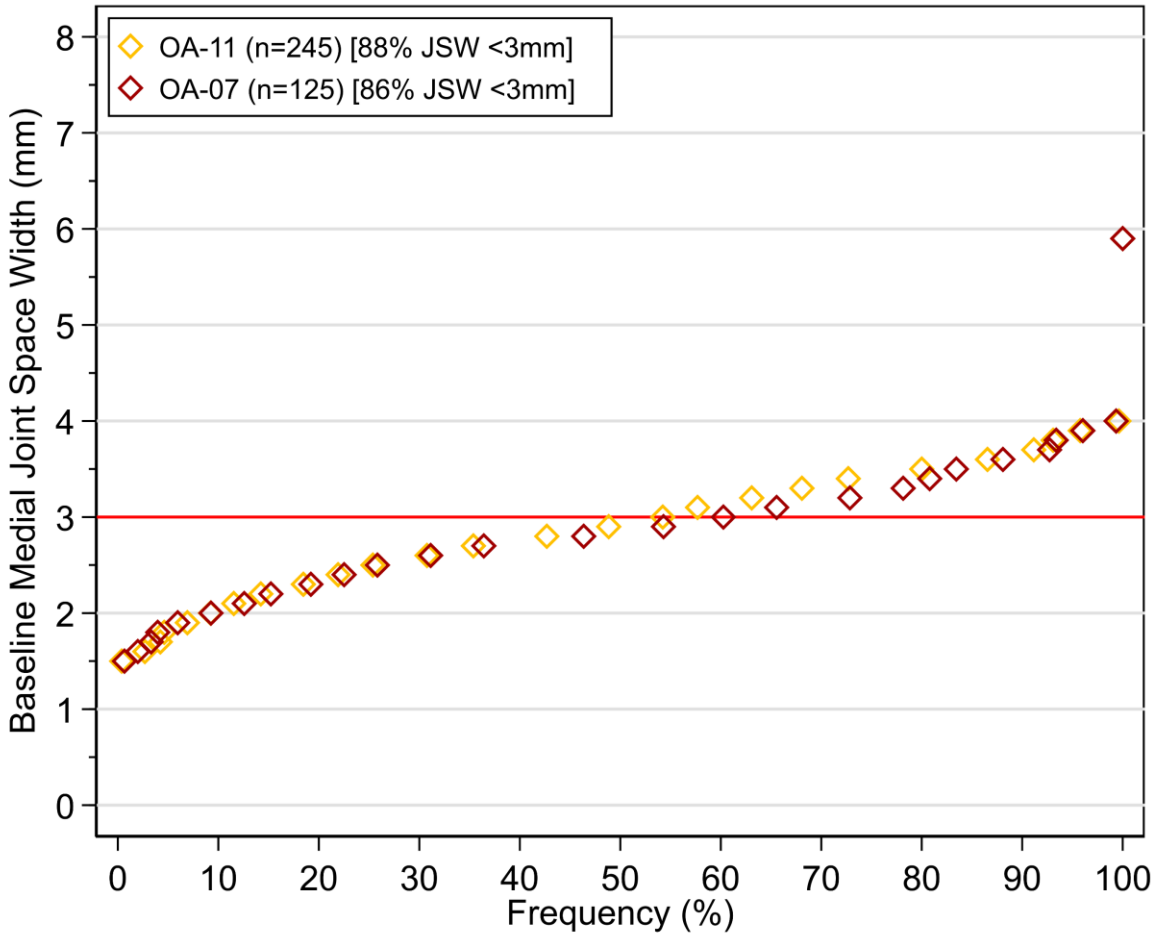


Baseline medial JSW for OA-11, OA-07, OA-02, OA-04, OA-10

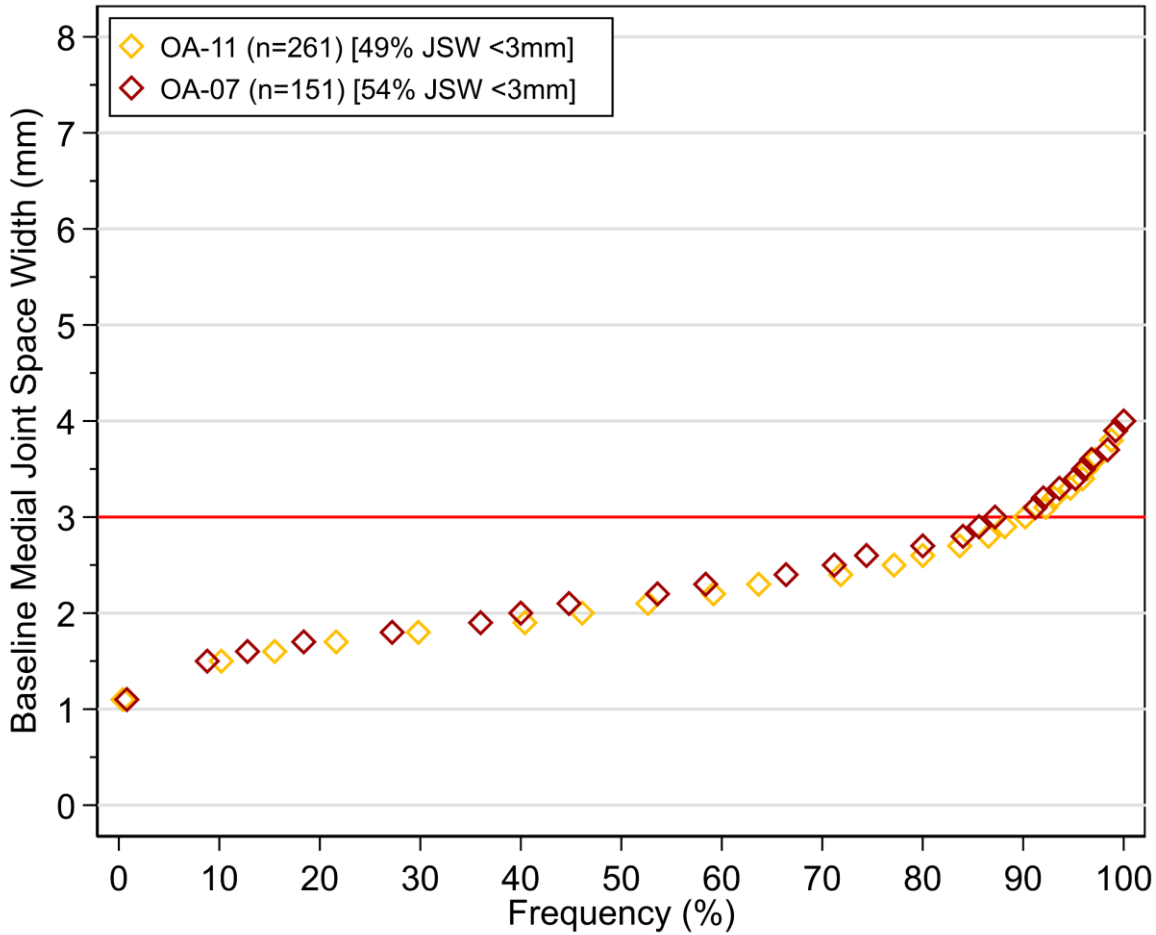


Cumulative Distribution of medial JSWs by KL Grade: OA-11 and OA-07

KL2

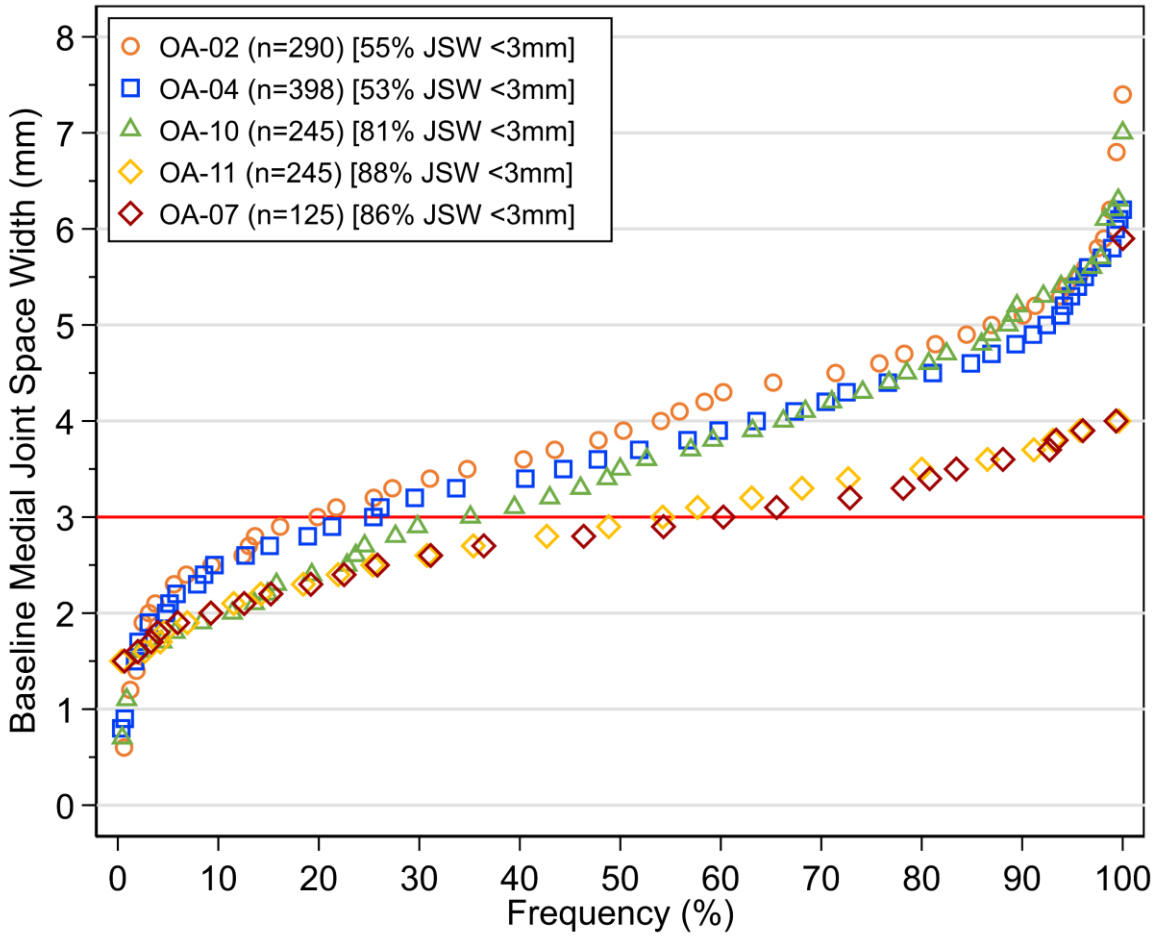


KL3

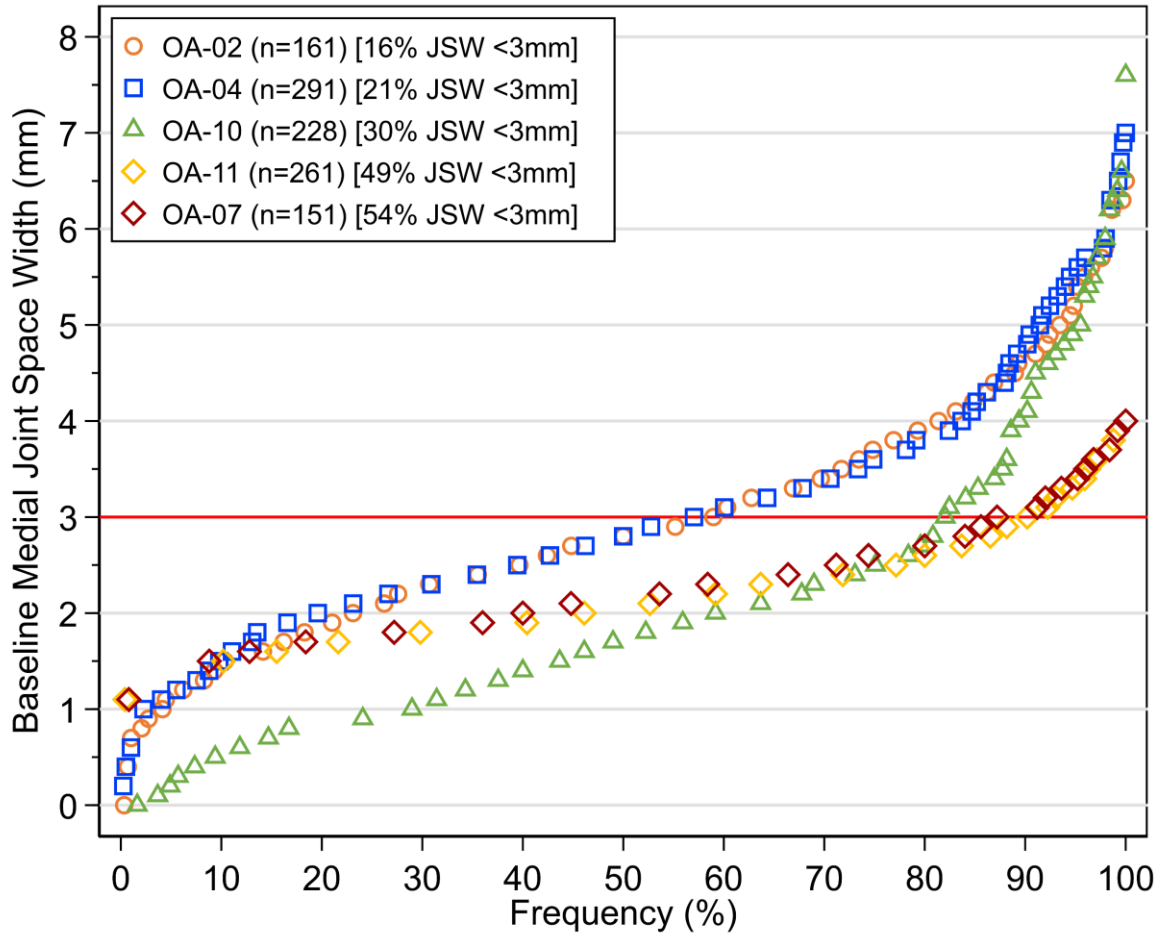


Cumulative Distribution of medial JSWs by KL Grade: OA-11, OA-07, OA-02, OA-04, and OA-10

KL2

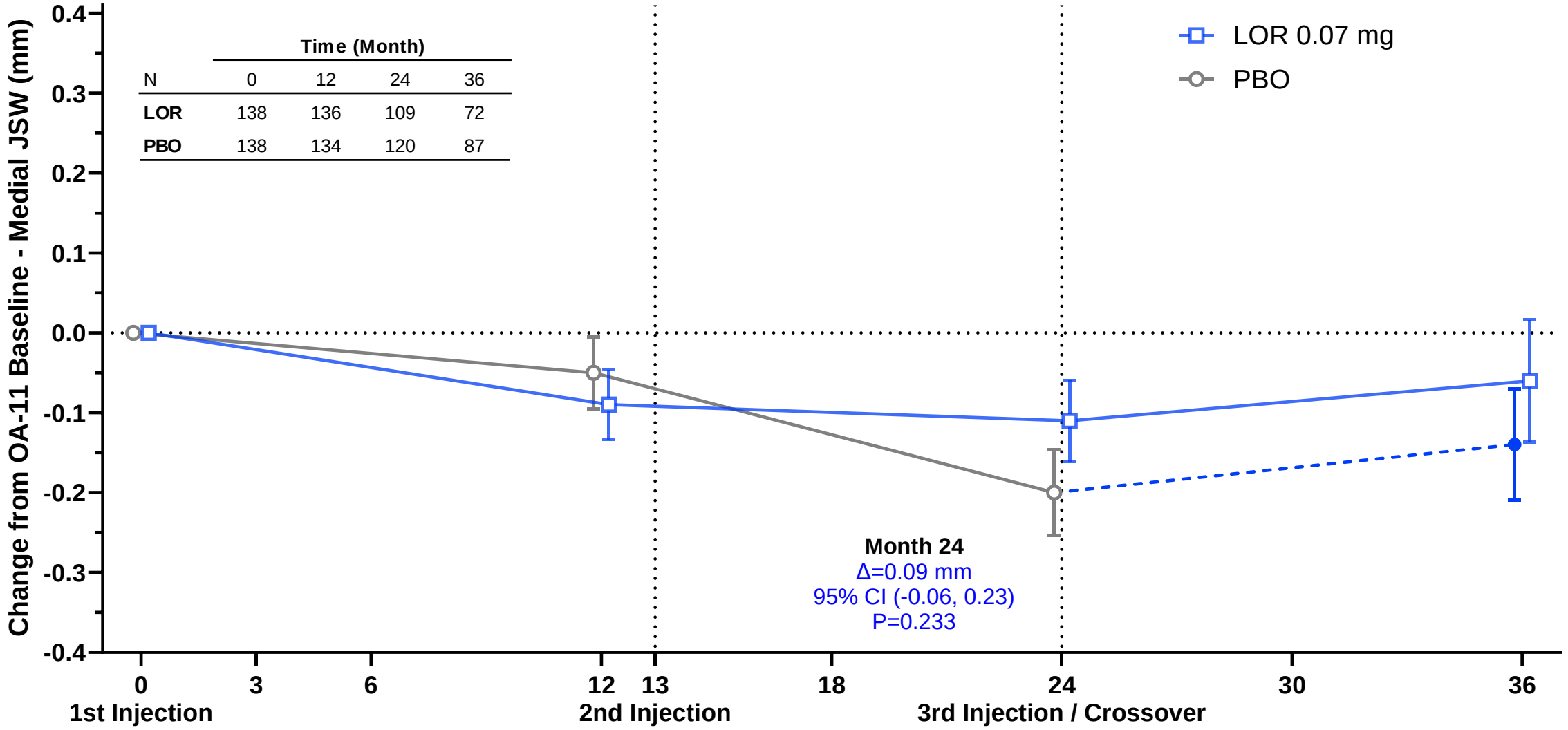


KL3



Medial JSW – Full Analysis Set (FAS)

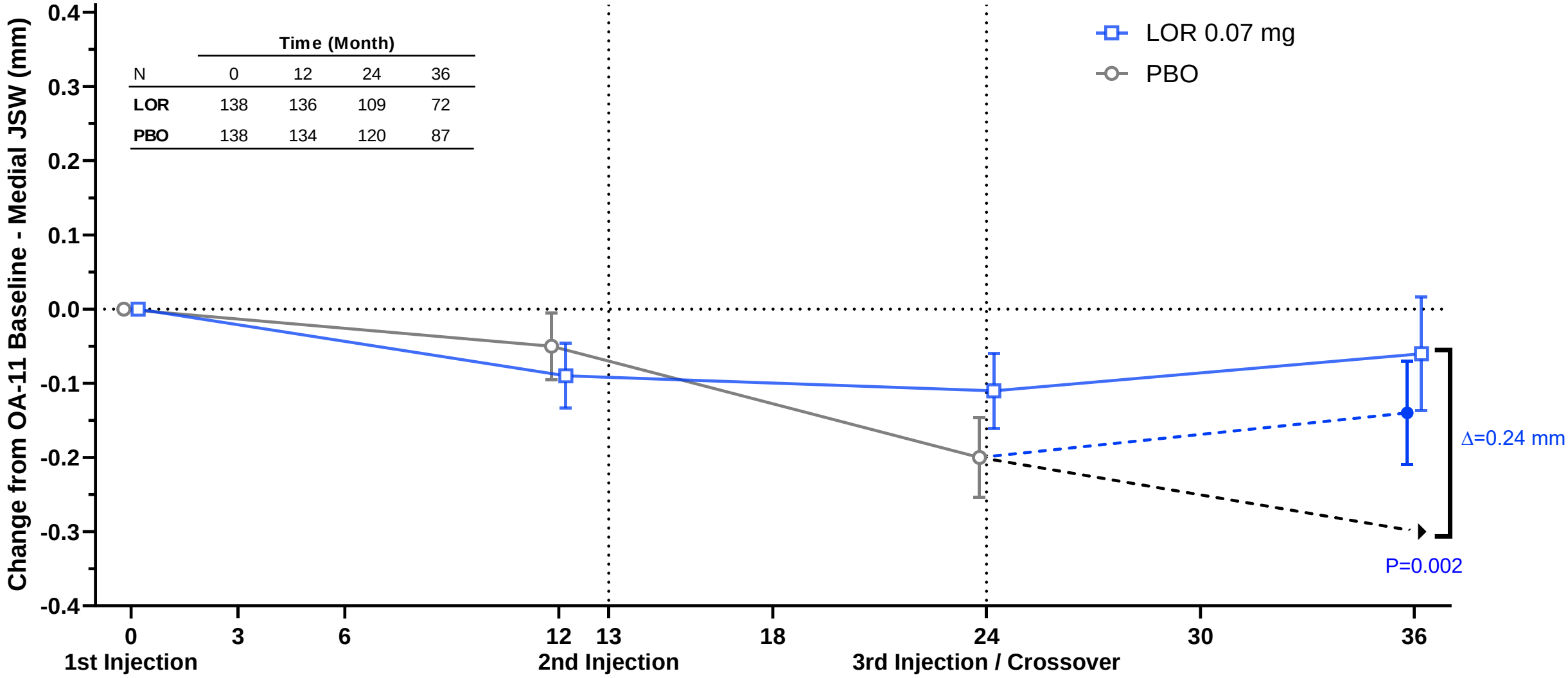
Medial JSW - FAS



OA-11 / OA-07 Medial JSW (mm) Change (FAS)

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

Medial JSW - FAS



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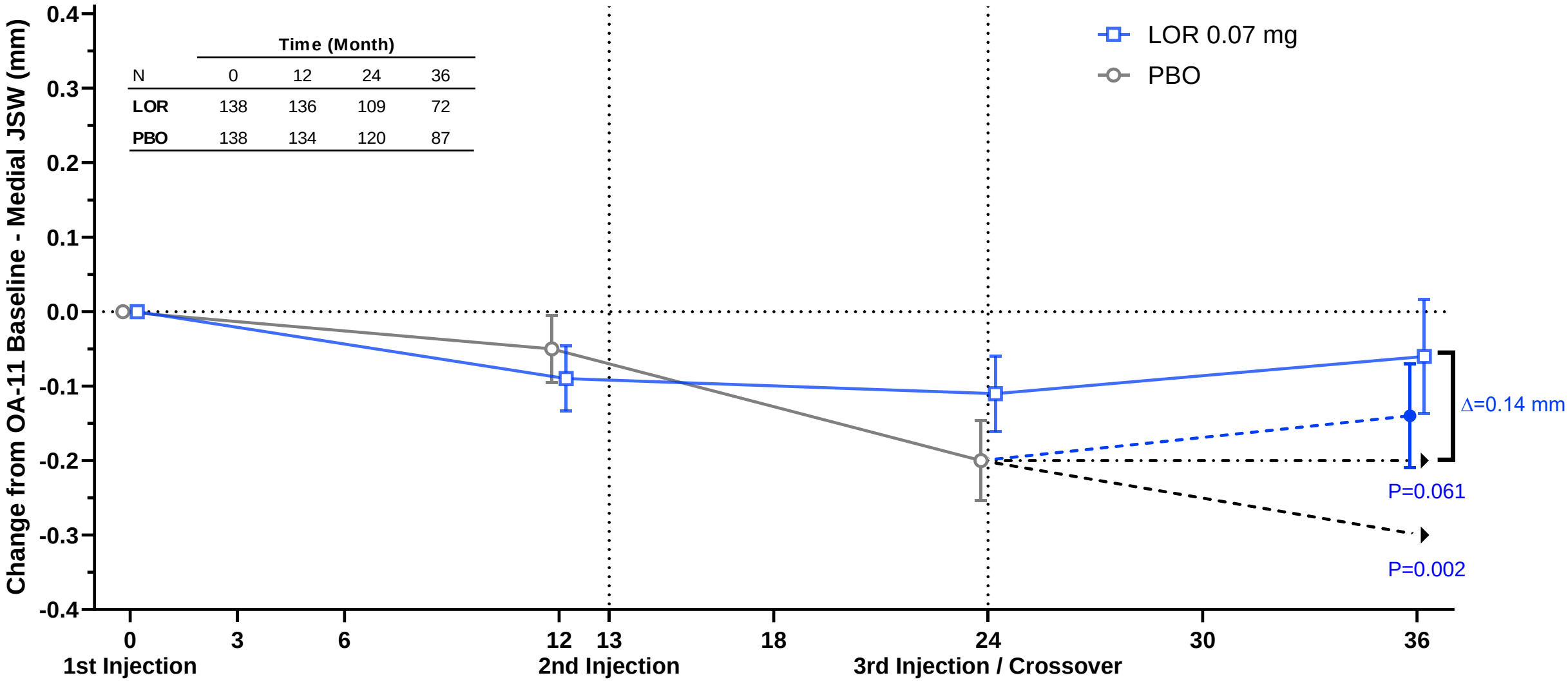
OA-11 / OA-07 Medial JSW (mm) Change (FAS)

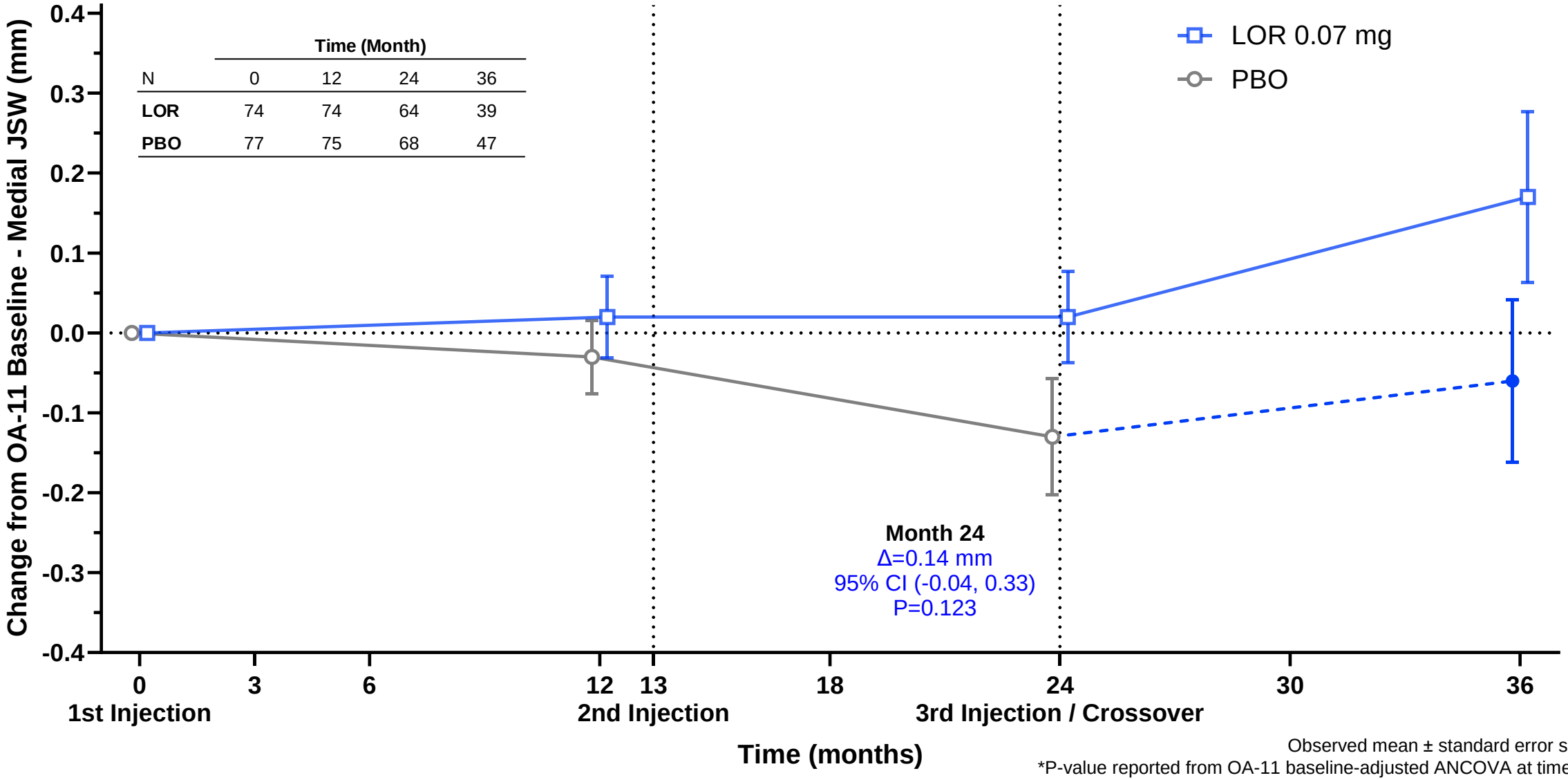
Medial JSW - FAS



OA-11 / OA-07 Medial JSW (mm) Change (FAS)

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

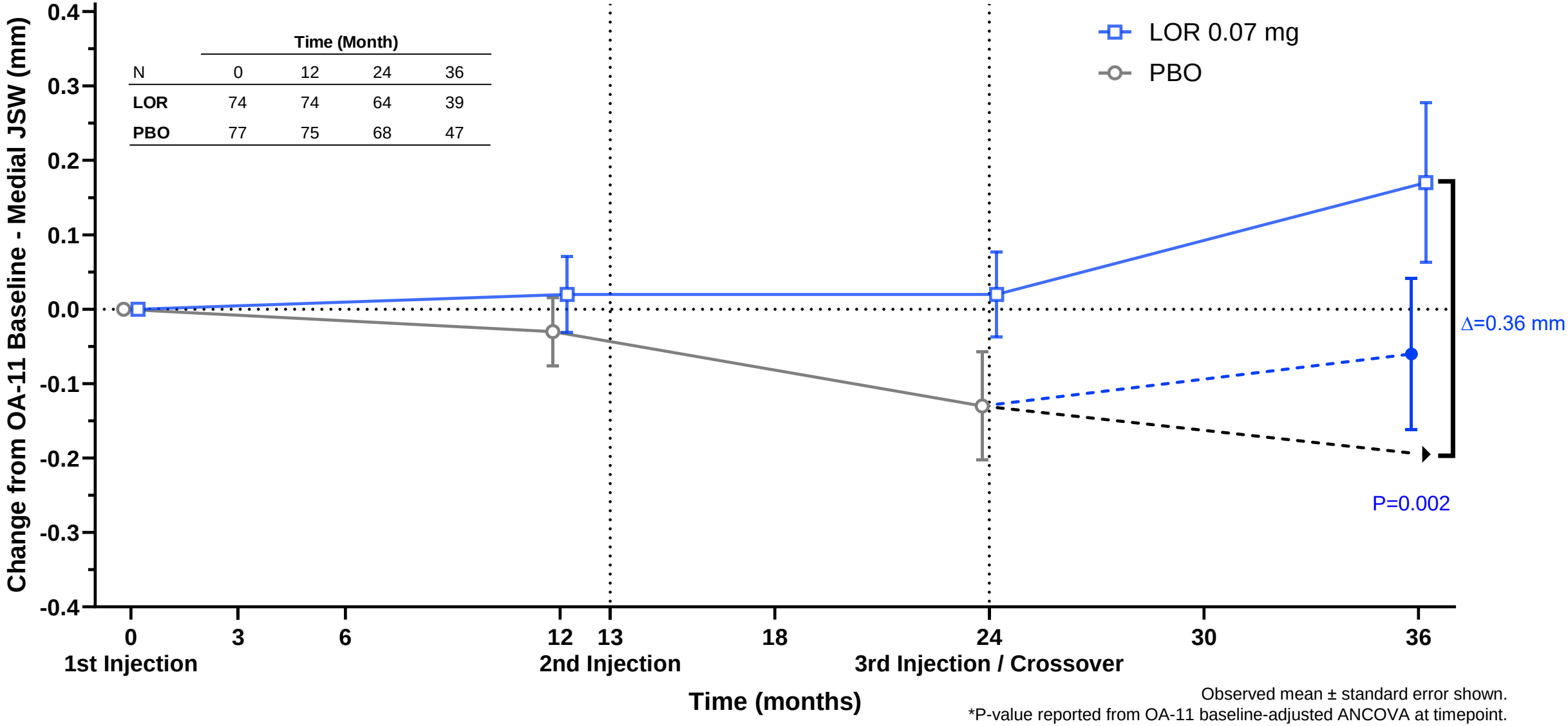
Medial JSW in KL2 - FAS



OA-11 / OA-07 Medial JSW (mm) Change KL2 Only (FAS)

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

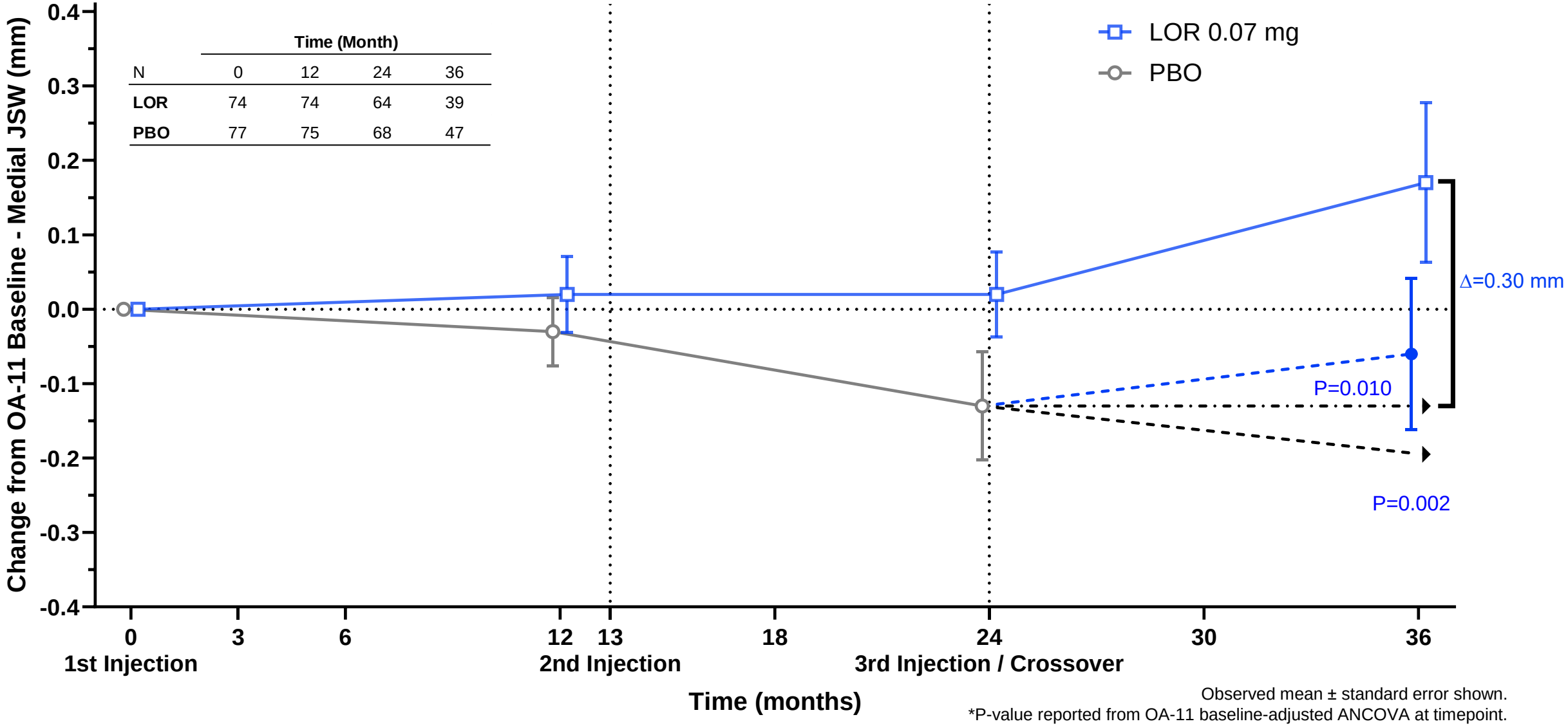
Medial JSW in KL2 - FAS



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

OA-11 / OA-07 Medial JSW (mm) Change KL2 Only (FAS)

Medial JSW in KL2 - FAS



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

OA-11 / OA-07 Medial JSW (mm) Change KL2 Only (FAS)

Medial JSW – 36 Month Completers

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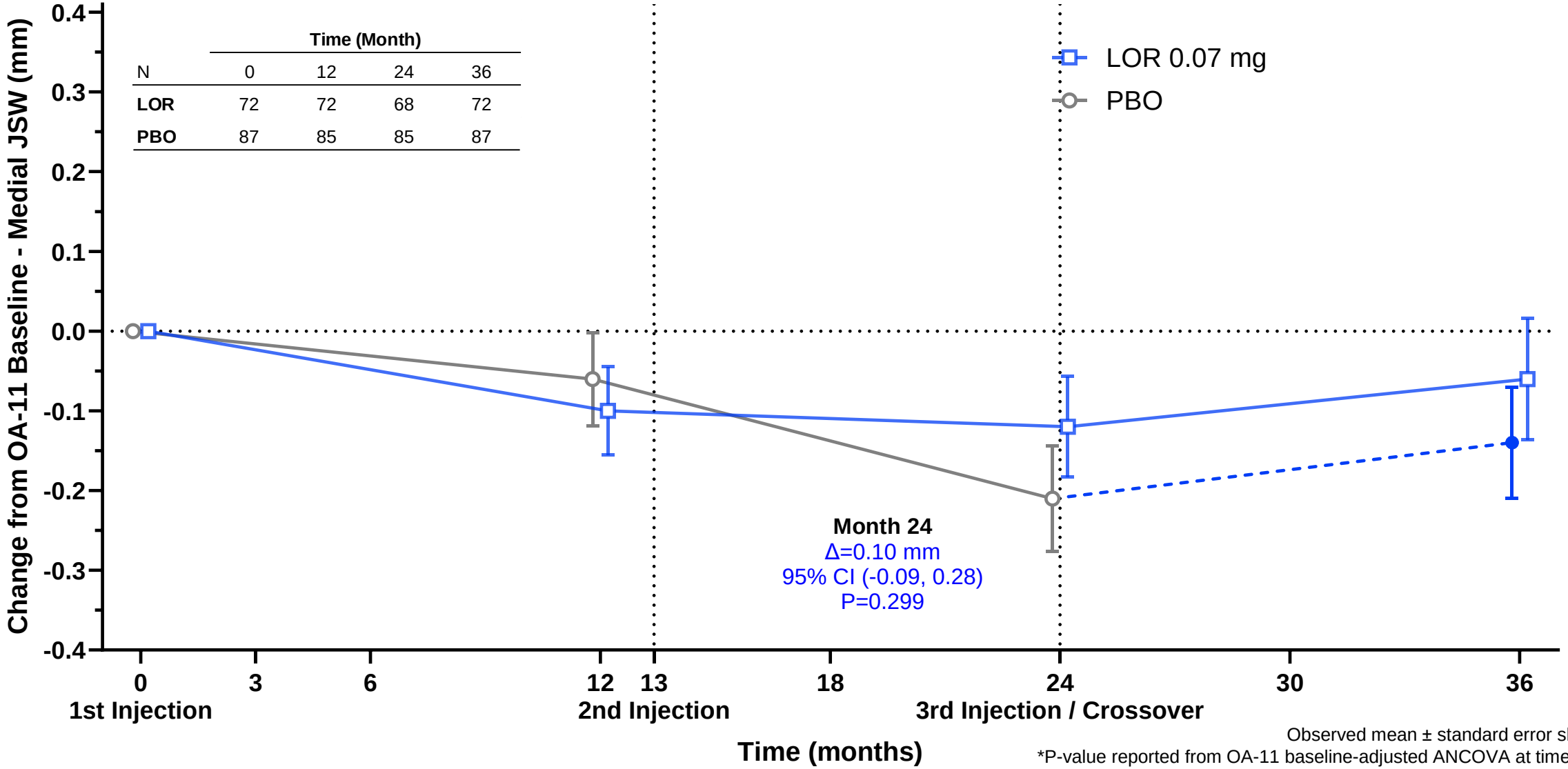
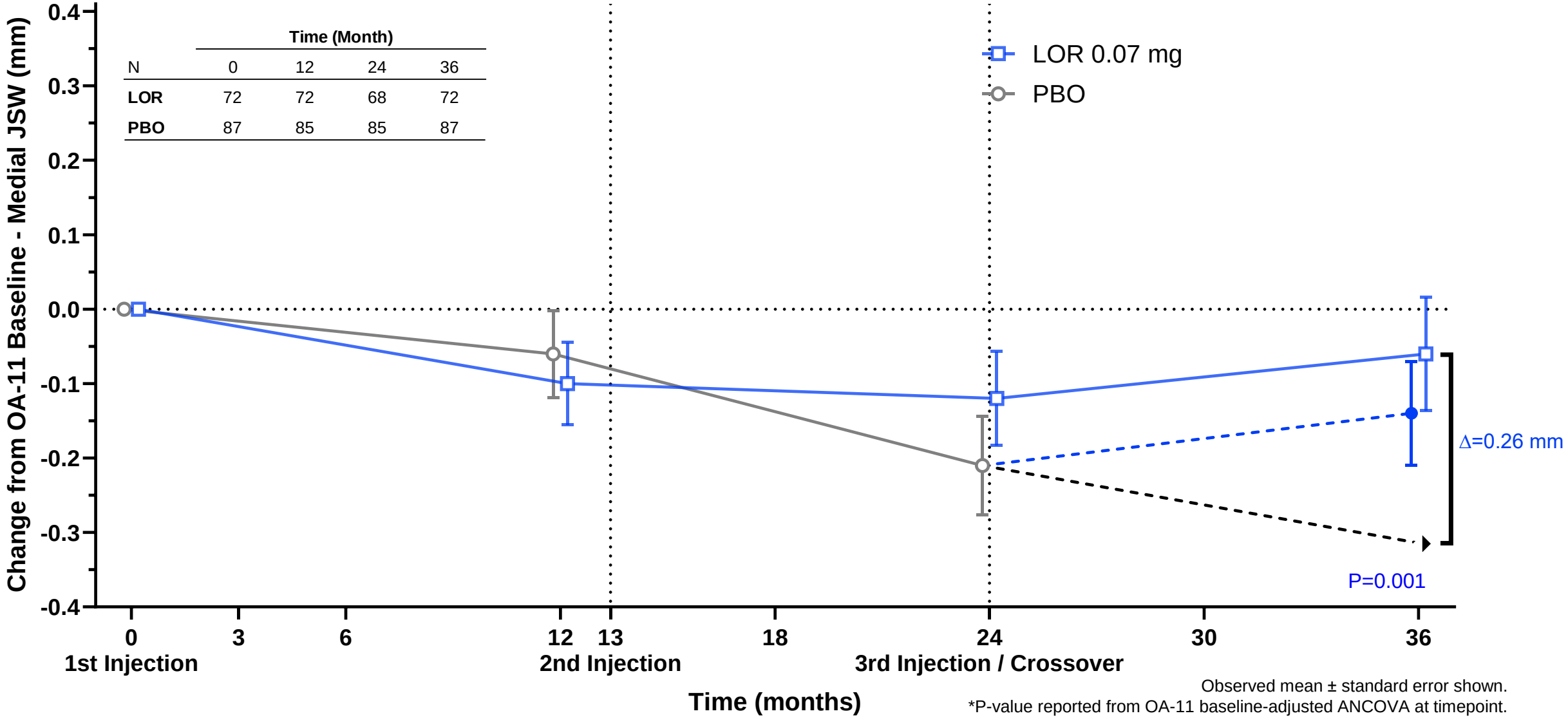


Observed mean ± standard error shown.
*P-value reported from OA-11 baseline-adjusted ANCOVA at timepoint.

OA-11 / OA-07 Medial JSW (mm) Change 3Yr Comp (FAS)

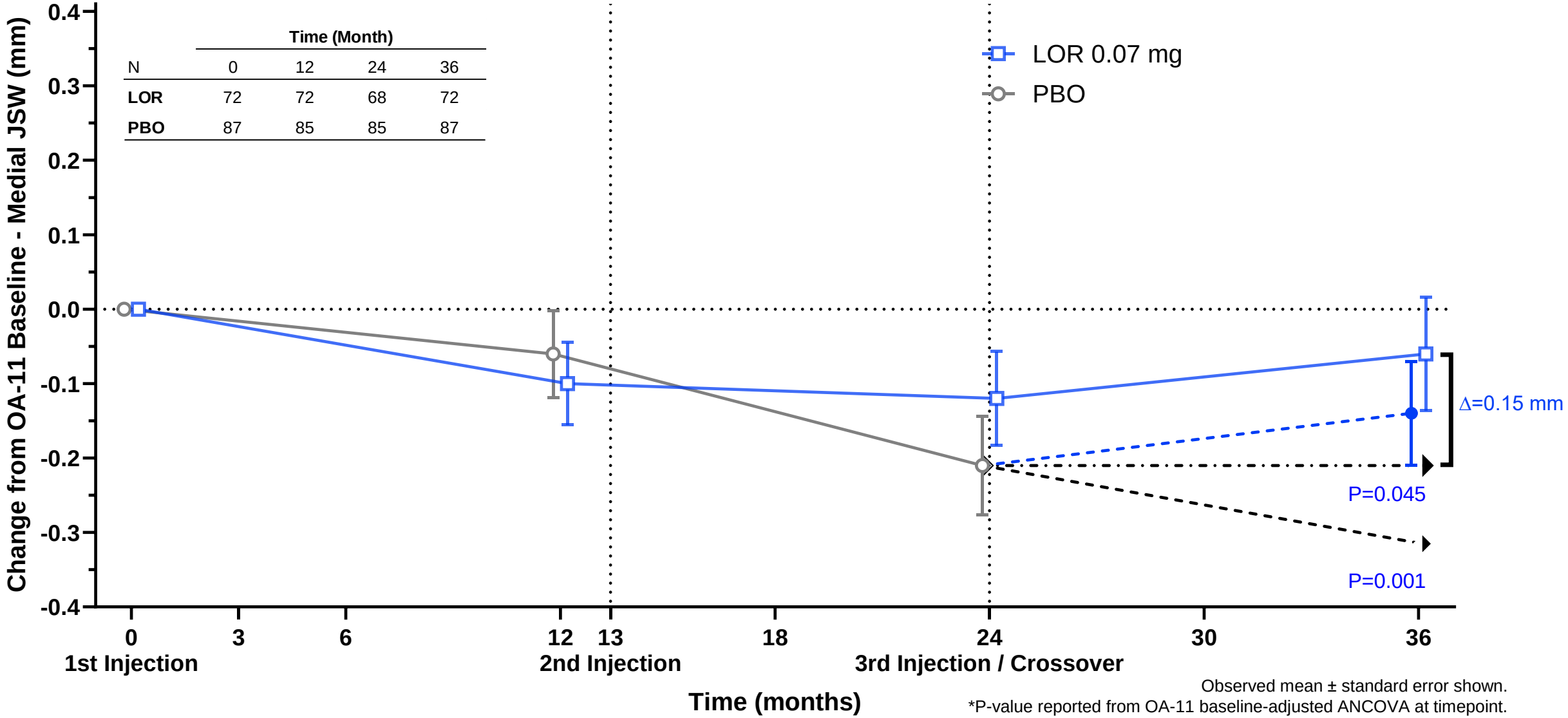
Medial JSW – 36 Months Completers



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

OA-11 / OA-07 Medial JSW (mm) Change 3Yr Comp (FAS)

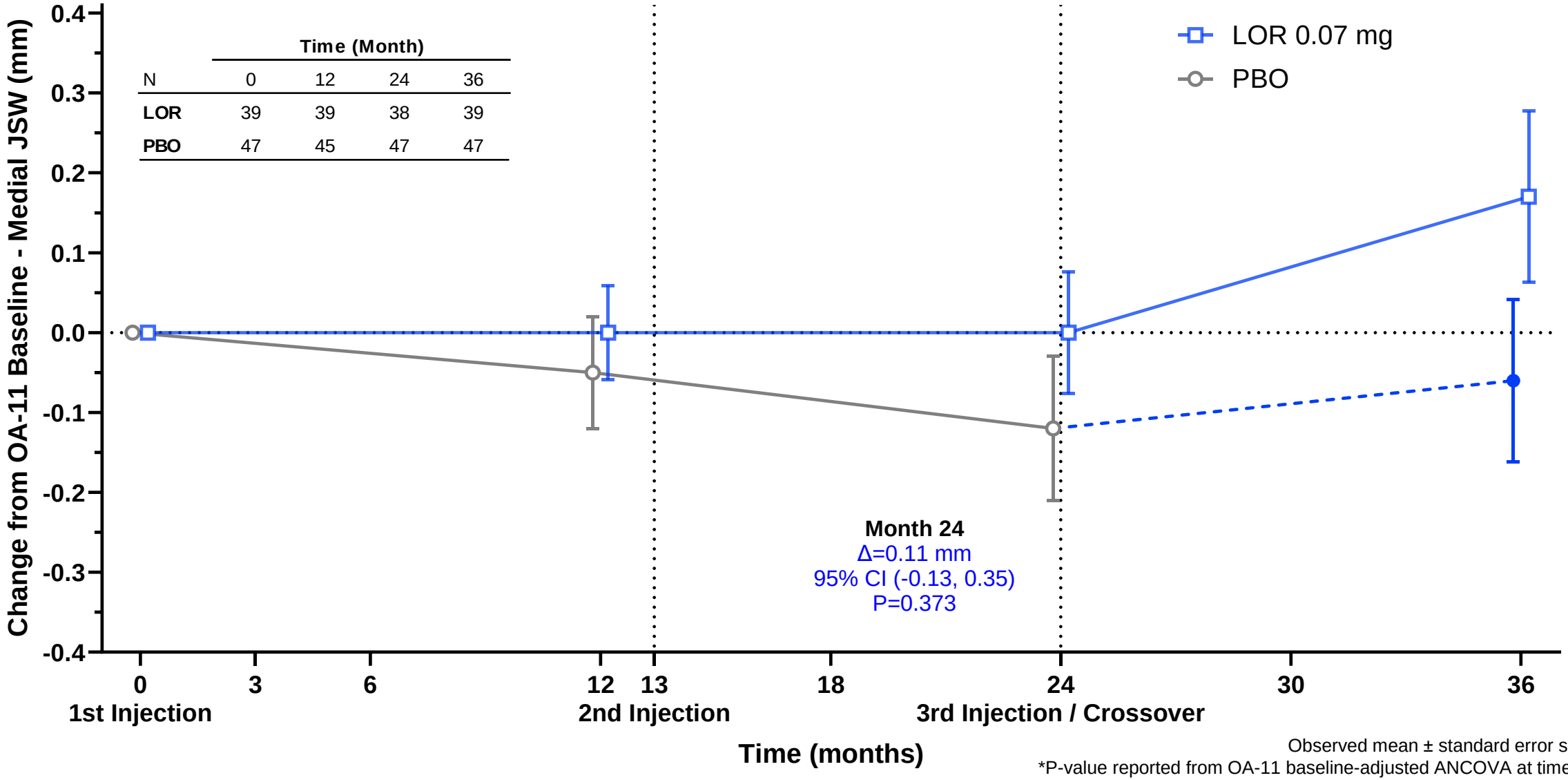
Medial JSW – 36 Months Completers



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

OA-11 / OA-07 Medial JSW (mm) Change 3Yr Comp (FAS)

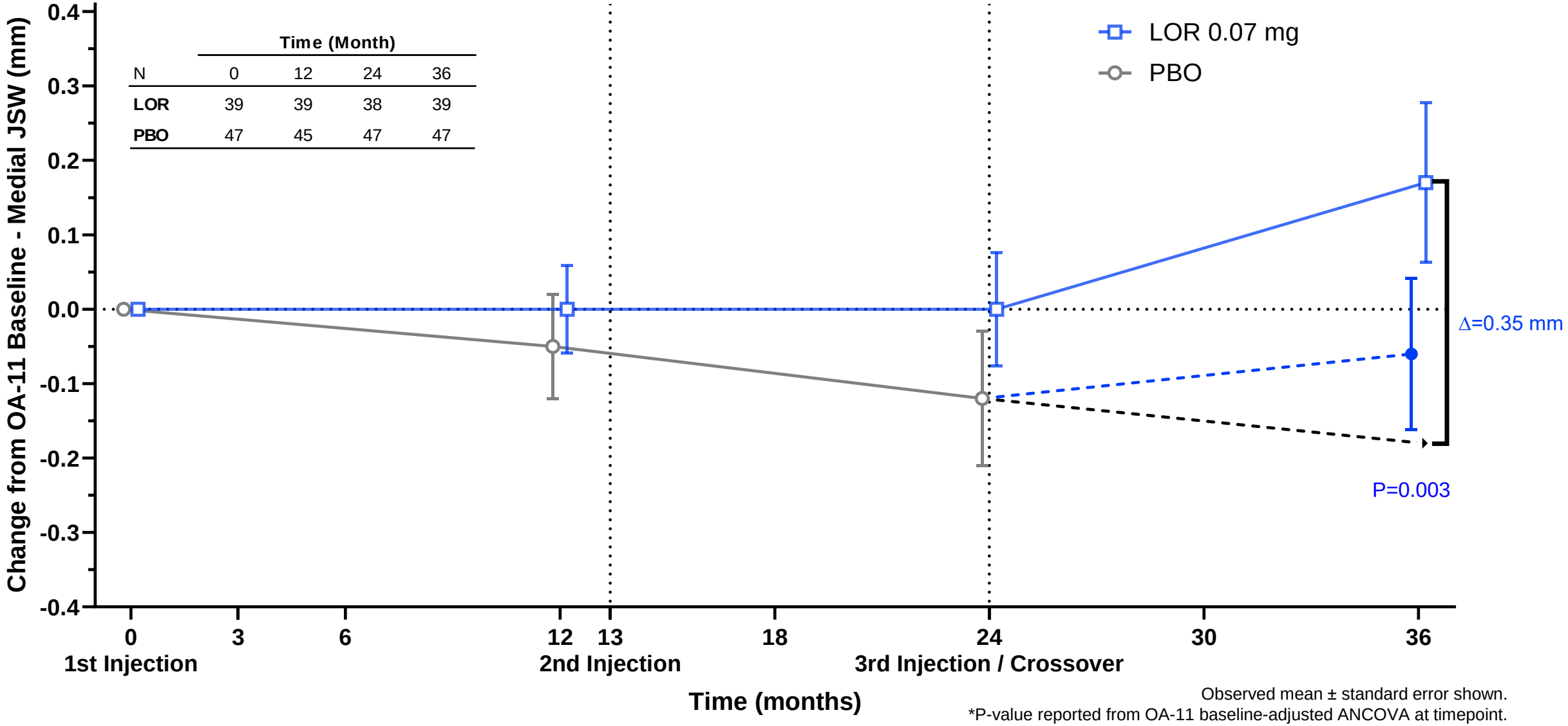
Medial JSW in KL2 - 36 Month Completers



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

OA-11 / OA-07 Medial JSW (mm) Change KL2 Only COMP (FAS)

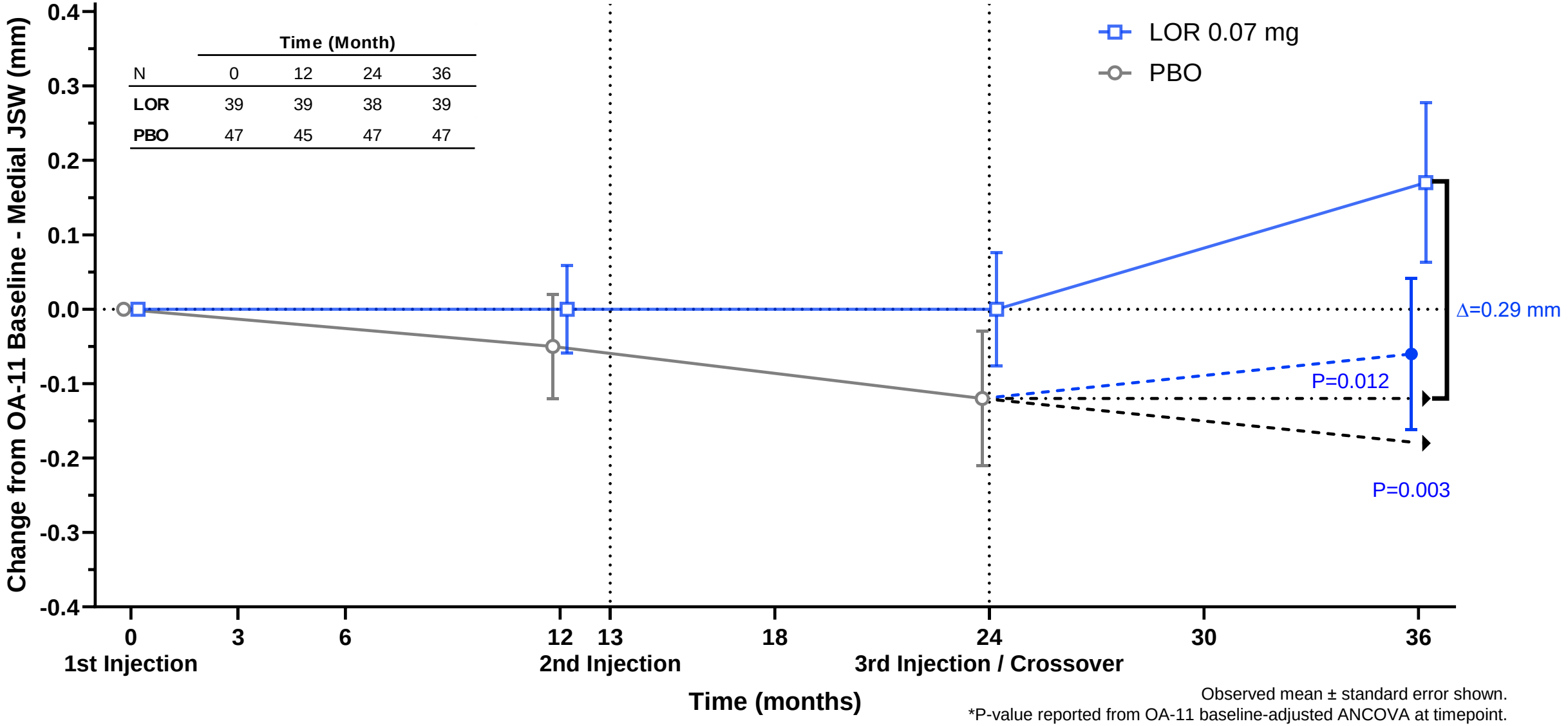
Medial JSW in KL2 - 36 Month Completers



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

OA-11 / OA-07 Medial JSW (mm) Change KL2 Only COMP (FAS)

Medial JSW in KL2 - 36 Month Completers

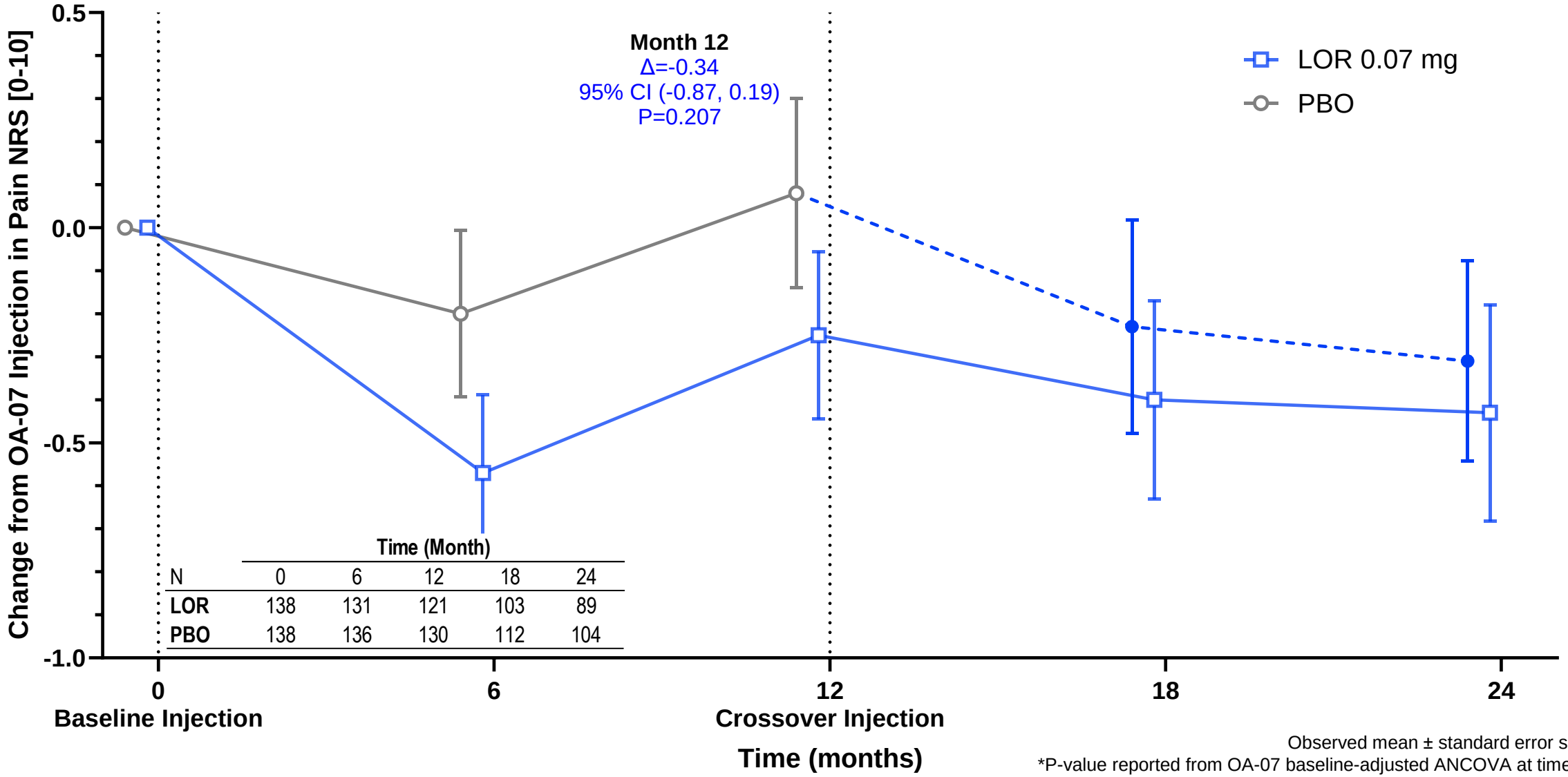


Observed mean ± standard error shown.
*P-value reported from OA-11 baseline-adjusted ANCOVA at timepoint.

OA-11 / OA-07 Medial JSW (mm) Change KL2 Only COMP (FAS)

Patient reported outcomes - FAS

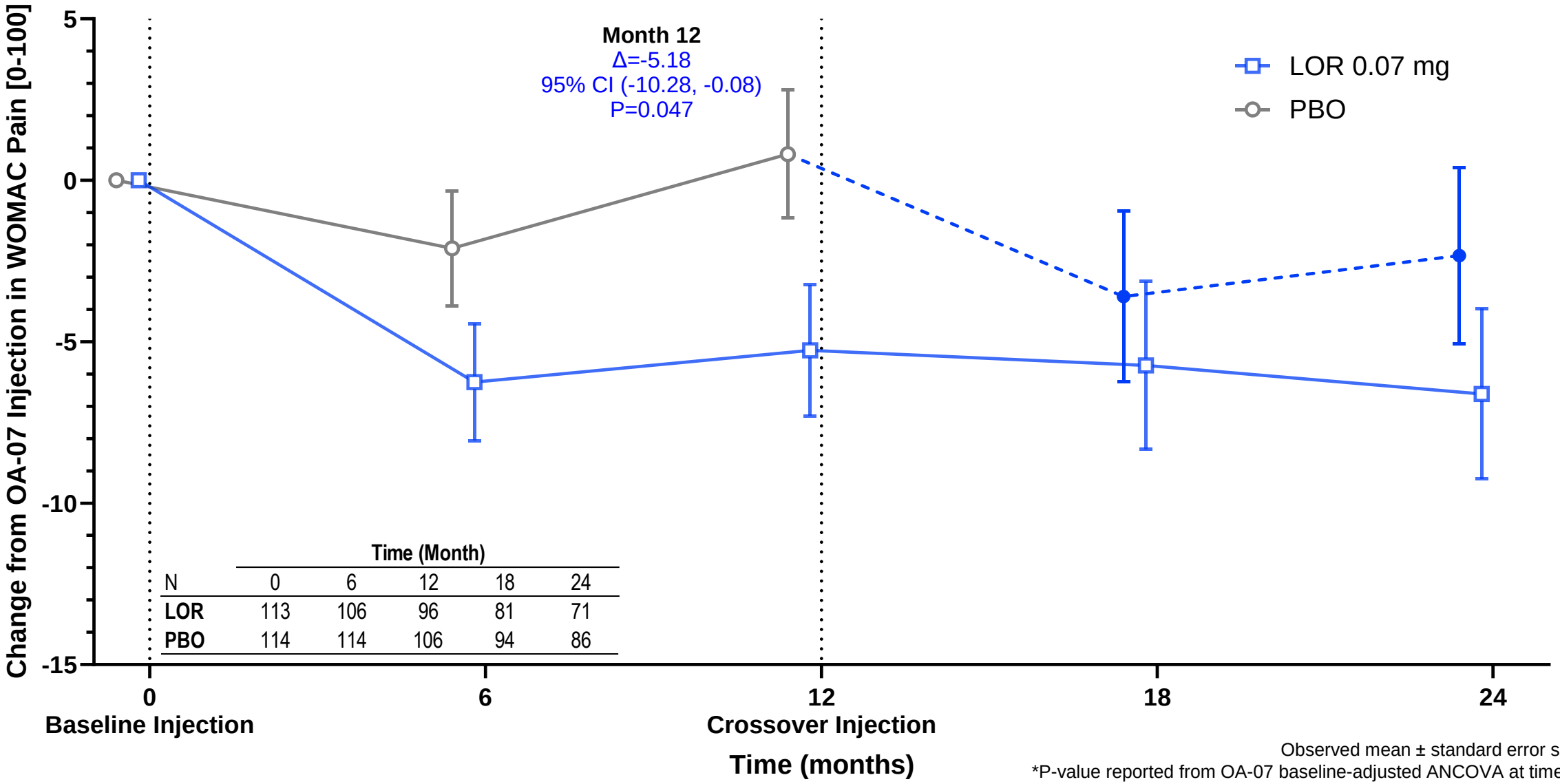
OA-07 Pain NRS Change from 2nd Injection



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

OA-07 Pain NRS [0-10] Change from OA-07 Baseline (FAS)

OA-07 WOMAC Pain Change from 2nd Injection

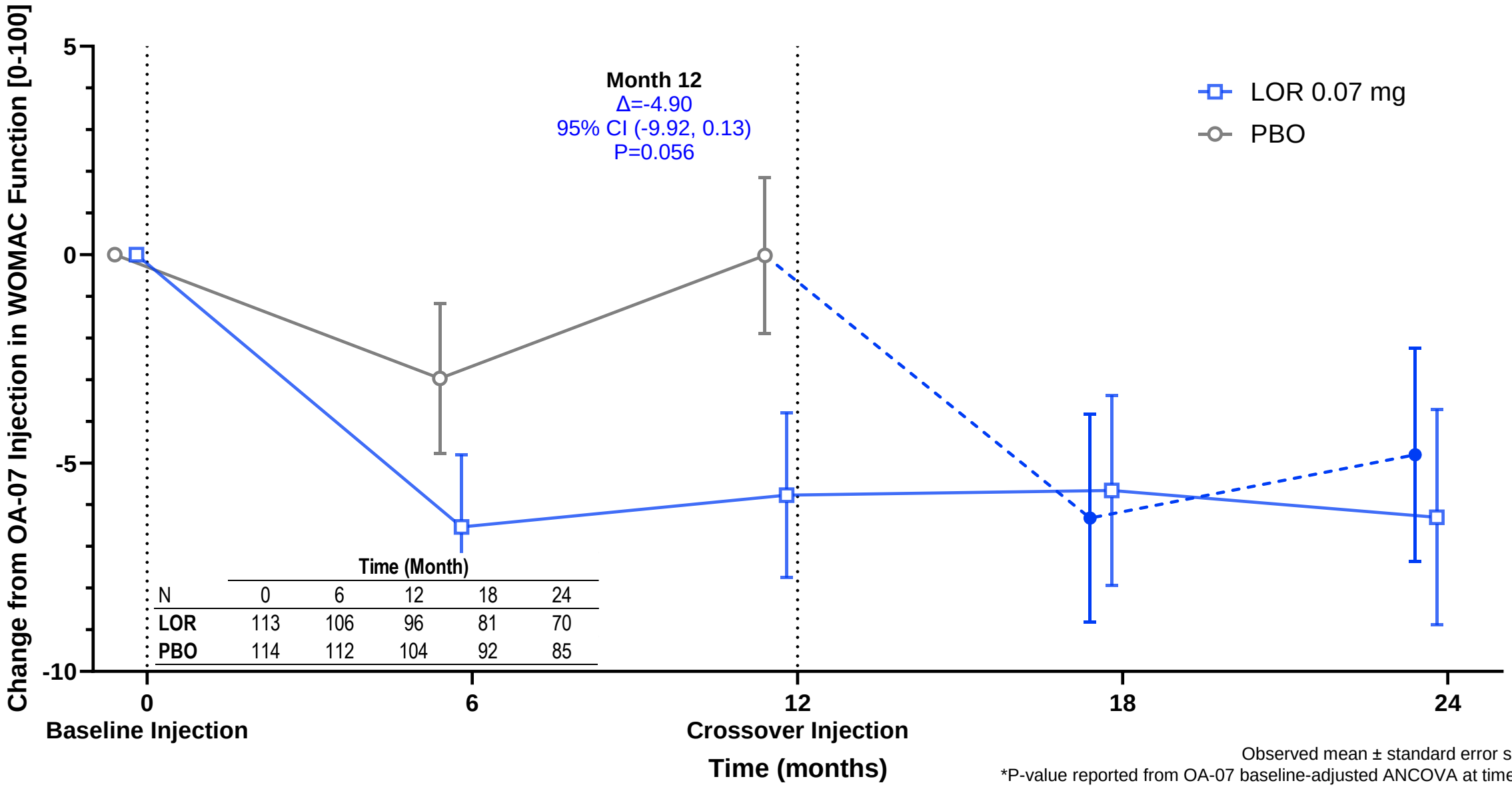


	Time (Month)				
N	0	6	12	18	24
LOR	113	106	96	81	71
PBO	114	114	106	94	86

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

OA-07 WOMAC Pain [0-100] Change from OA-07 Baseline (FAS)

OA-07 WOMAC Function Change from 2nd Injection



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

OA-07 WOMAC Function [0-100] Change from OA-07 Baseline (FAS)

Conclusions

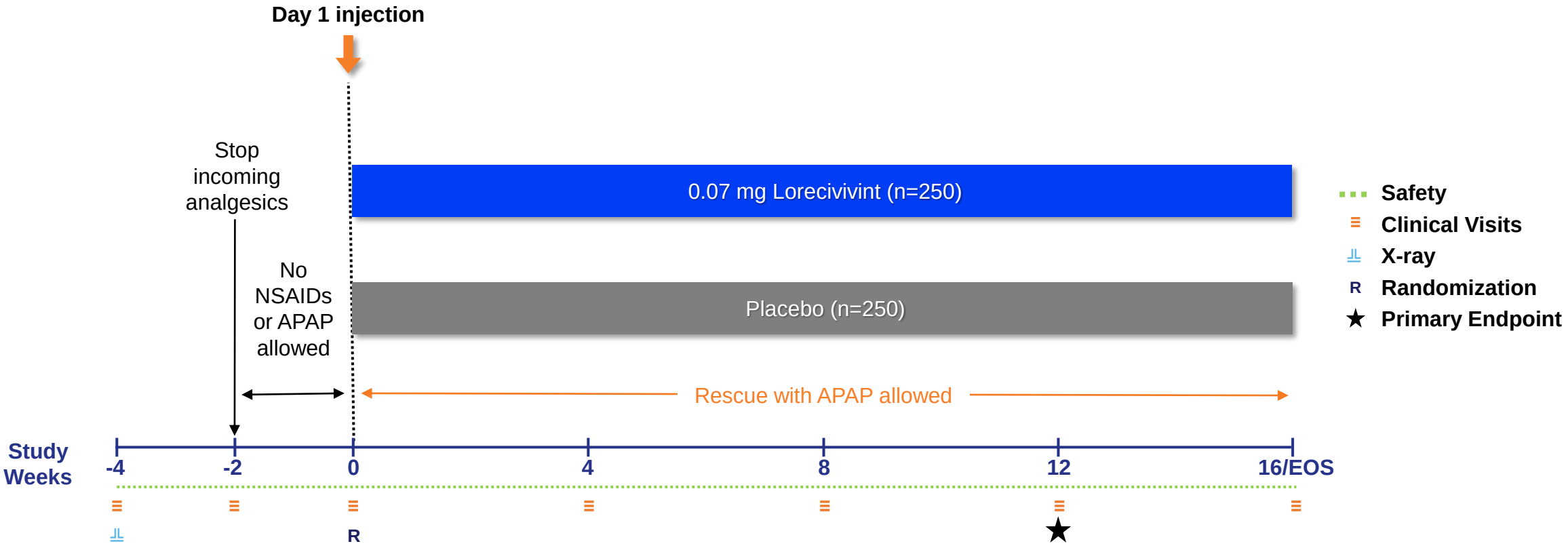
- OA-07 met its primary objective in this structurally advanced knee OA cohort
  - Structural benefit over 3 years with multiple LOR injections, especially in KL2 knee OA patients

- Repeated yearly LOR injections provided structural benefit and improved PROs at 24 months, with additional benefits following third injection seen through 36 months compared to PBO imputations

- PBO patients crossing to LOR at 24 months, showed both structural benefit and PRO improvements at 36 months, reinforcing potential treatment effects

- LOR seemed safe and well-tolerated, consistent with previous LOR trials

OA-21 Trial Design



Population: moderate-severe pain (4-9/10), N: ~ 500
BMI <35, targeting 70% KL2 and 30% KL3. For KL3, OARSI JSN [0-1]
Primary Endpoint: Pain NRS at Week 12
Secondary Endpoints: WOMAC Function and Patient Global Assessment at Week 12

Thank you

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