Lorecivivint Delayed Time to Pain and Function Worsening Compared to Placebo

Evaluation of Knee OA Symptom Progression Outcomes in a Phase 3 Trial (OA-07)

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ACR Convergence
Where Rheumatology Meets

Disclosure

- Yusuf Yazici, MD: Chief Medical Officer, Biosplice Therapeutics, Inc.
- Christopher J. Swearingen, PhD: VP Biometrics, Biosplice Therapeutics, 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, is currently in development as intra-articular knee OA treatment

- Objective of OA-07 study was to evaluate efficacy and safety of repeat IA injections of 0.07 mg LOR
  - Patient reported outcomes – Western Ontario & McMaster Universities Osteoarthritis Index (WOMAC) Pain & WOMAC Function
  - Radiographic outcome – Medial Joint Space Width (JSW)

Total Knee Replacement

- Indication for TKR based on symptoms (pain and function)
- Delaying worsening of symptoms potentially delays need for TKR
- Structural damage, worsening of damage associated with worse pain and function
- TKR as an outcome in an RCT virtually impossible to do
  - 3-5 years duration
  - Placebo control for 3-5 years
  - Impact of race, ethnicity, geography, insurance on TKR utilization

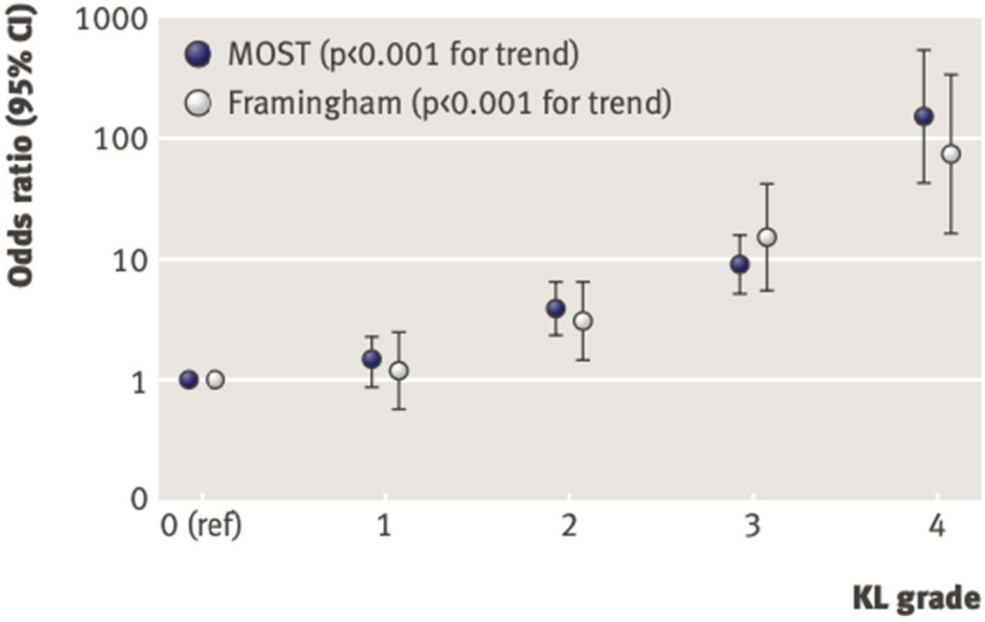


Fig 1 | Associations of frequent knee pain with Kellgren and Lawrence (KL) grade among people with two knees discordant for frequent knee pain status. No of case knees (those with frequent knee pain) and control knees (those without frequent knee pain) shown beneath graph for each KL grade. Note that y axis is logarithmically scaled

Neogi T et al. BMJ 2009

Total Knee Replacement

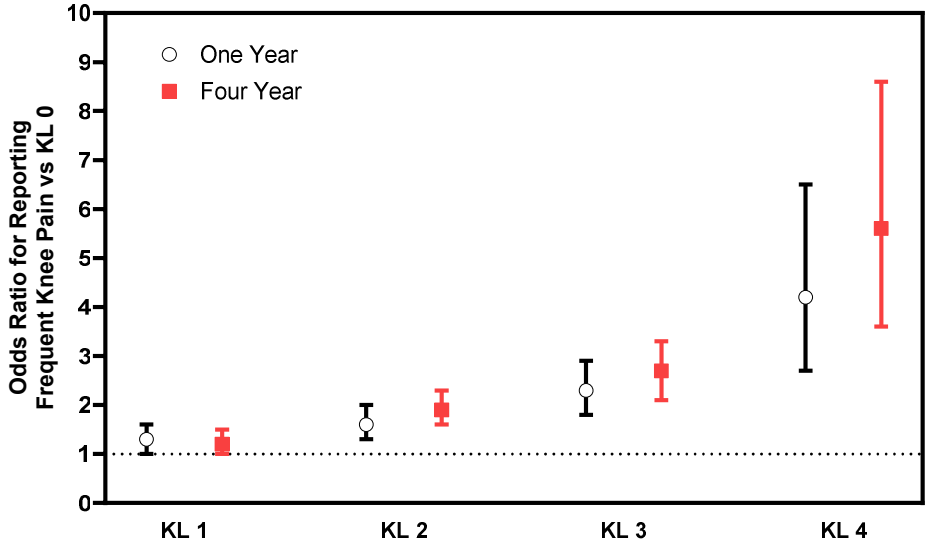
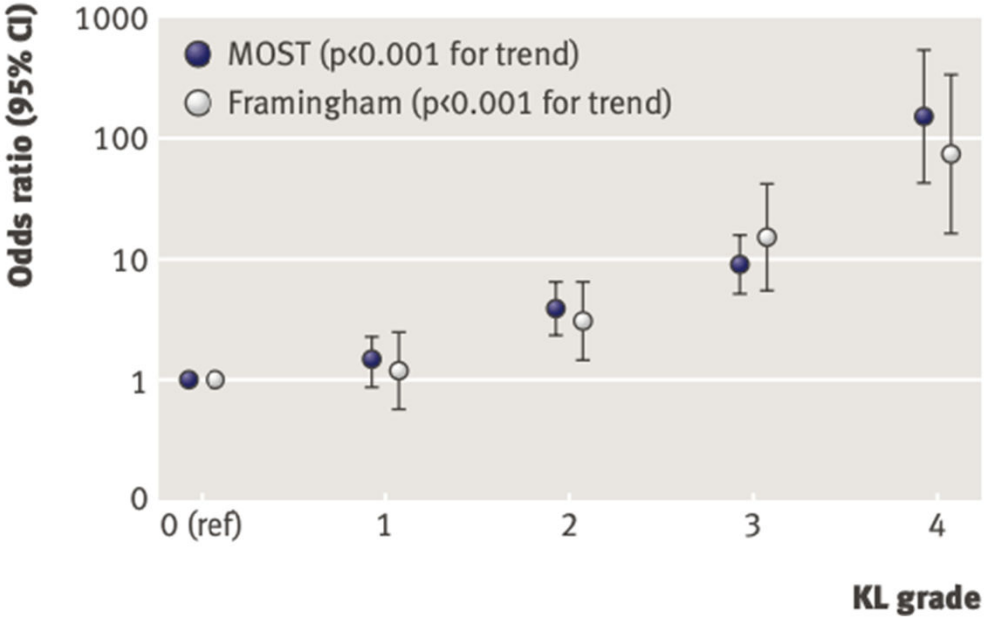


Figure based upon reported analysis from Lo G et al #2090 ACR Convergence 2025



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Adding to this previous work, an OAI analysis presented today demonstrated similar relationship between KL grade and reporting of Frequent Pain at both 1 and 4 years

Neogi T et al. BMJ 2009

Osteoarthritis: Structural Endpoints for the Development of Drugs, Devices, and Biological Products for Treatment

Guidance for Industry

DRAFT GUIDANCE

August 2018

Clinical/Medical

II. CONSIDERATIONS FOR DEVELOPMENT

Sponsors should consider the following regarding structural endpoints for developing medical products for the treatment of OA:

- FDA recognizes that OA can be a serious disease with an unmet medical need for therapies that modify the underlying pathophysiology of the disease and potentially change its natural course to prevent long-term disability. However, there are several ongoing issues with developing such products, including the multifactorial and complex etiopathogenesis of the disease, the well-recognized discordance between structural changes and signs/symptoms/function, the lack of standard definitions of disease progression, and, correspondingly, the absence of endpoints to reliably assess the ability of a product to alter OA disease progression.

- Because of the complex and variable pathologic changes through which OA impairs function and leads to long-term disability and/or joint replacement, at this time it is unclear what magnitude of change in structural endpoints would translate to a clinically meaningful benefit to patients (i.e., reliably predict both reduced pain and increased function or prolonged time to end-stage disease). Thus, no structural endpoints have been used for traditional or accelerated approval in OA to date.

- To accept structural endpoints as valid outcome measures for accelerated approval, there should be substantial confidence, either based on empirical evidence from randomized, controlled comparisons from clinical trials and/or based on a comprehensive understanding of the disease process and product mechanism of action, that an effect on the candidate structural endpoint will reliably predict an effect on the clinical outcomes of interest.[5] The ultimate goal of treatments related to inhibition of structural damage or targeting the underlying pathophysiology associated with OA is to avoid or significantly delay the complications of joint failure and the need for joint replacement, and also to reduce the deterioration of function and worsening of pain.

At this time, the ability of treatment effects on common measures of structural progression to reliably predict treatment effects on direct measures of how patients function and feel, has not been established. Therefore, FDA welcomes efforts to address the above considerations and is open to work with all stakeholders on such programs.

- OA can be a serious disease
- “well-recognized” discordance between structural changes and signs/symptoms/function
- Unclear what magnitude of change in structure translates to clinical benefit
- Empirical evidence needed from randomized controlled trials
- Goal to avoid or significantly delay joint failure and the need for replacement as well as worsening pain and function
- Ability of treatment to demonstrate benefit on how a patient feels, functions and survives has not been established

Advancing Disease Modification Endpoints

1

- Proposed a Composite Endpoint capturing a Patient's ability to Function, Feel and Survive
- Total Knee Replacement (TKR), a "direct measure" of how the knee survives, combined with Severe Disease States:

  WOMAC Pain ≥ 75% alone or in combination with WOMAC Function ≥ 75%

2

- Defined Virtual Knee Replacement (vKR) criteria as a surrogate for TKR
- Incorporated both Pain and Quality of Life Comparative Evaluation to Previous Visit
- Knee Pain Worsening Conveyed Increased Likelihood of vKR above and beyond Pain Status

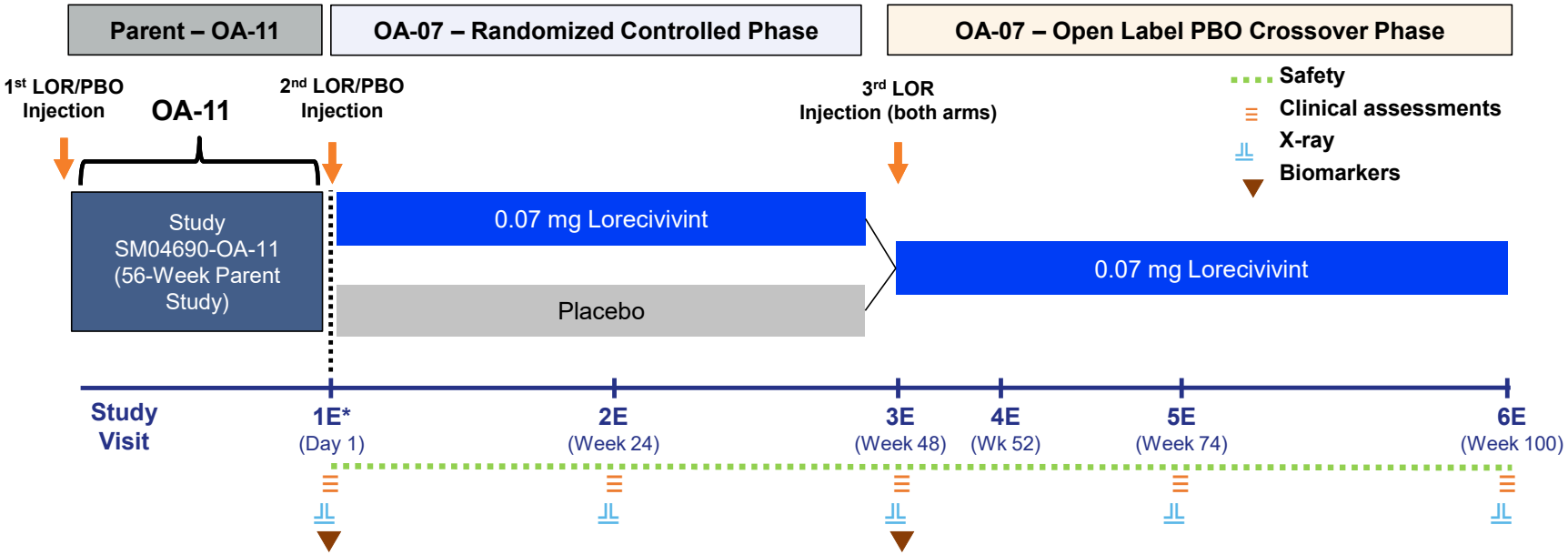
3

- Defined Symptom Progression Endpoint to show "delay in symptom worsening":

  Worsening in WOMAC Pain ≥ 10 points and no improvement in WOMAC Function > 9 points
- Evaluated Symptom Progression with structure data from 5-year clinical trial

1. Kim Y et al. *Arth Care Research* 2022; 74:1154-1162
2. Kwoh CK et al. *OAC* 2025; Aug 6 (online)
3. Conaghan PG et al. *OAC* 2025; 33:383-390

Methods: OA-07 Trial Design



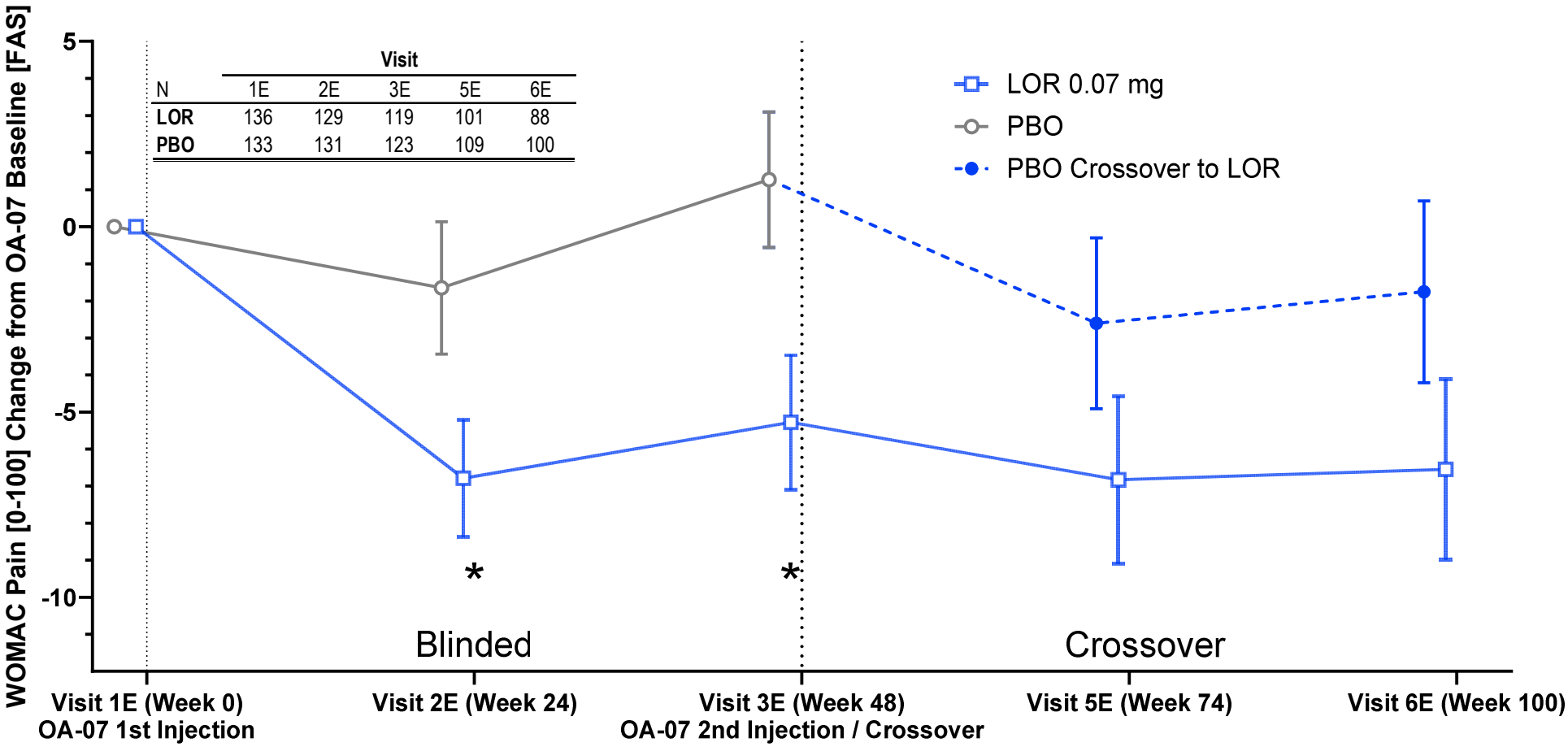
- ~50% of OA-11 patients enrolled into the OA-07 trial
- Patient characteristics similar between OA-11 and OA-07 trial
- Patients and investigators remained blinded to initial treatment throughout

Methods: Disease Progression Analysis

- Defined Symptom Progression endpoints similar to Conaghan
  - Worsening in WOMAC Pain [0-100] increase by ≥ 10 points
  - Worsening in WOMAC Function [0-100] increase by > 9 points
  - Worsening in both WOMAC Pain and Function

- Multivariable Cox regression to estimate progression differences between Lorecivivint and placebo, adjusting for age and Kellgren-Lawrence Grade

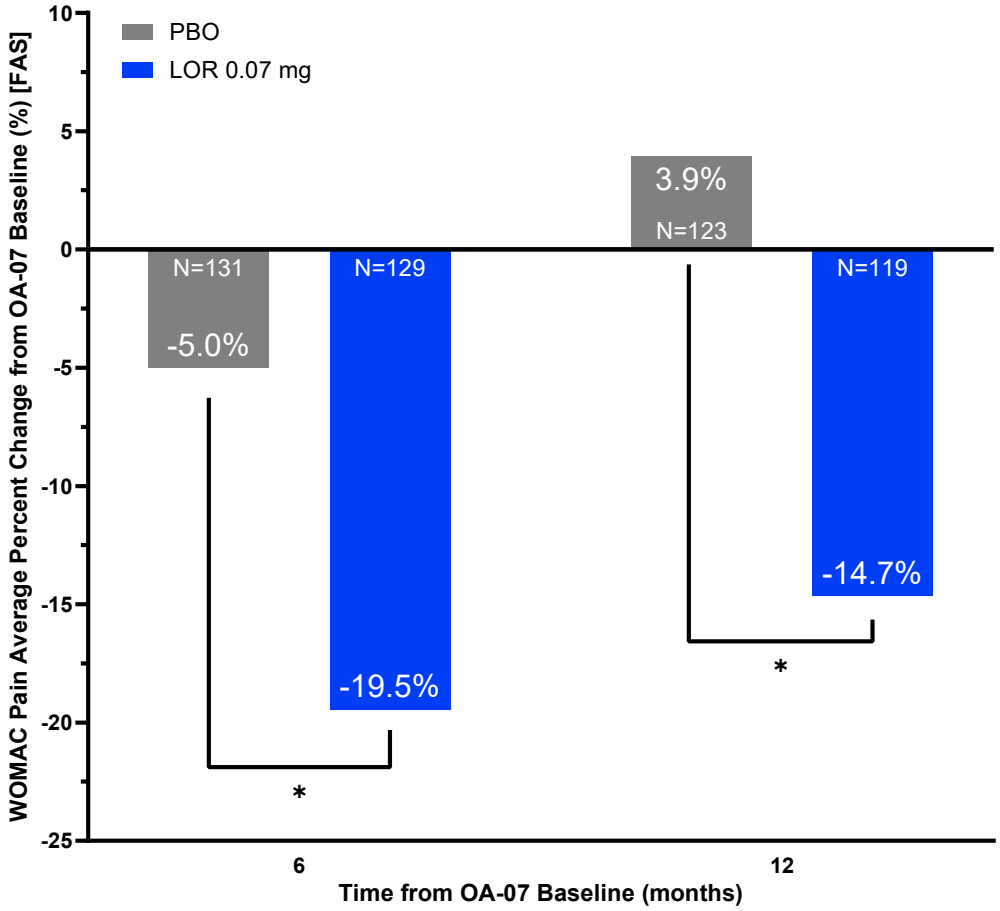
Results: WOMAC Pain Change from Baseline



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 Osteoarthritis Index; **LOR**=lorecivivint; **PBO**=placebo

Results: WOMAC Pain Change from Baseline (%)



Observed mean change repreesented as percent change shown.
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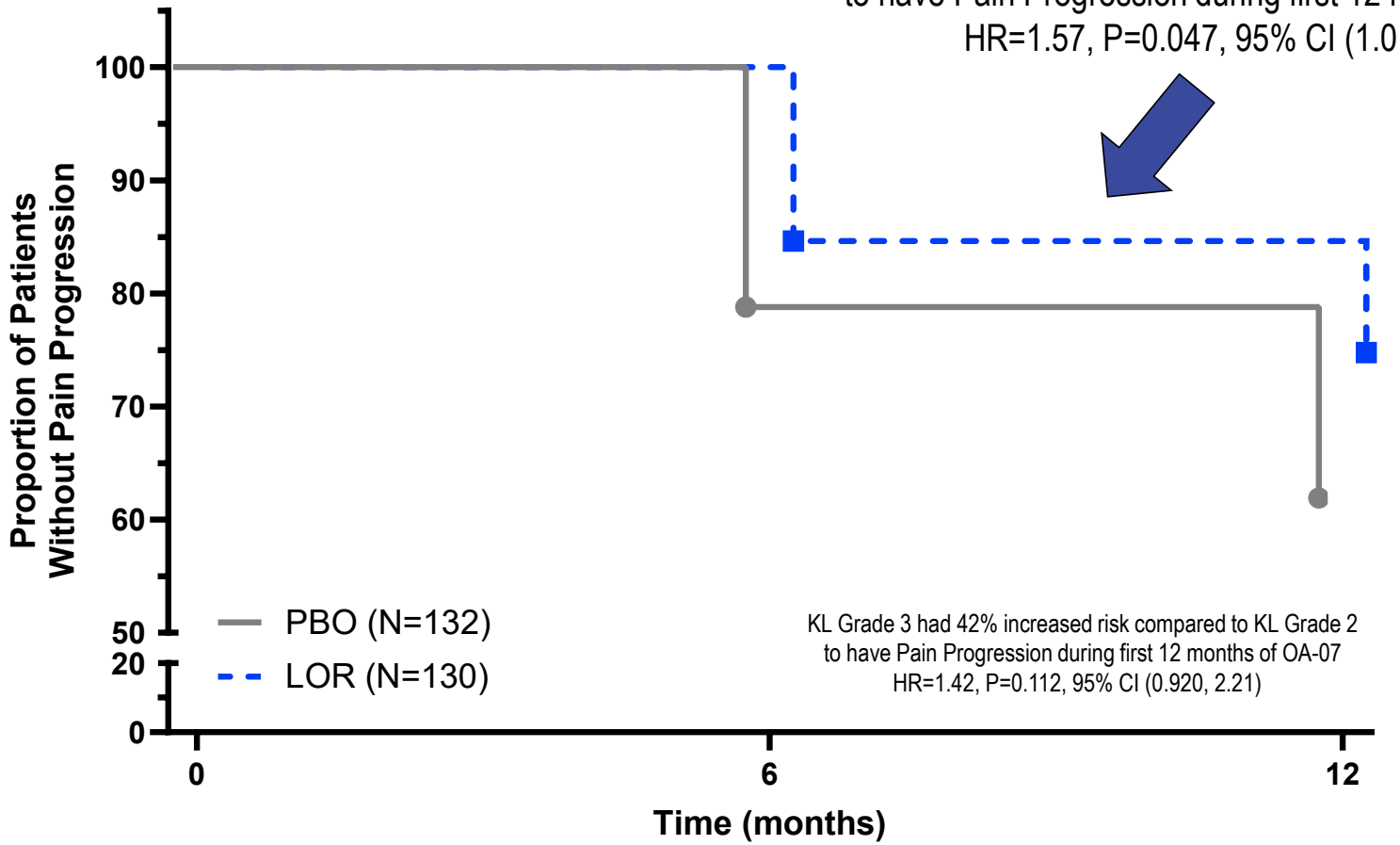
FAS=Full Analysis set; **WOMAC**=Western Ontario & McMaster Universities Osteoarthritis Index; **LOR**=lorecivivint; **PBO**=placebo

Results: LOR Significantly Reduced Pain Progression Risk

Change in WOMAC Pain [0-100] ≥ 10 points

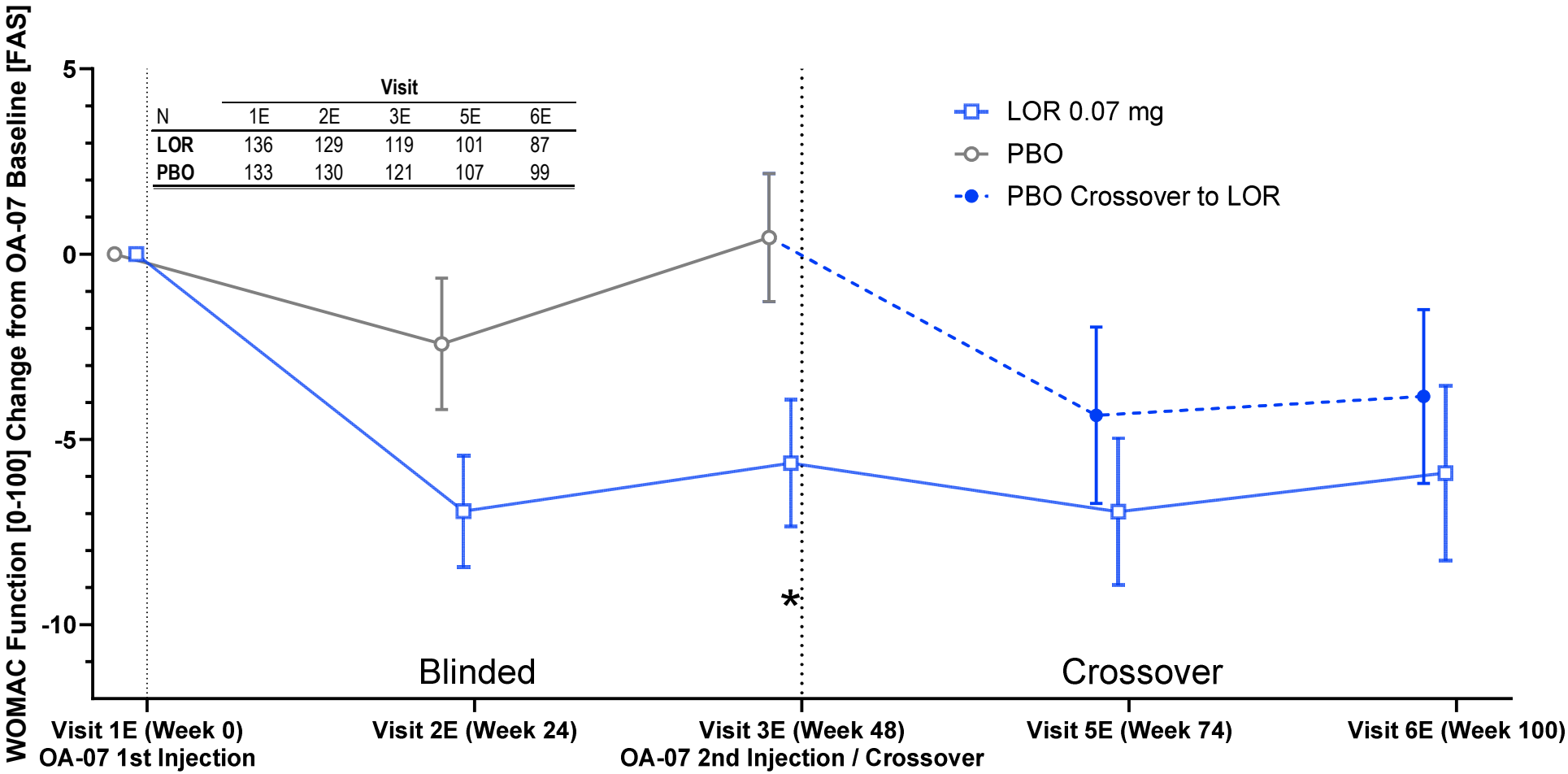
PBO had 57% increased risk compared to LOR
to have Pain Progression during first 12 months of OA-07
HR=1.57, P=0.047, 95% CI (1.01, 2.46)



KL Grade 3 had 42% increased risk compared to KL Grade 2
to have Pain Progression during first 12 months of OA-07
HR=1.42, P=0.112, 95% CI (0.920, 2.21)

WOMAC=Western Ontario & McMaster Universities Osteoarthritis Index; **LOR**=lorecivivint; **PBO**=placebo; **KL**=Kellgren-Lawrence; *Post-hoc Analysis*

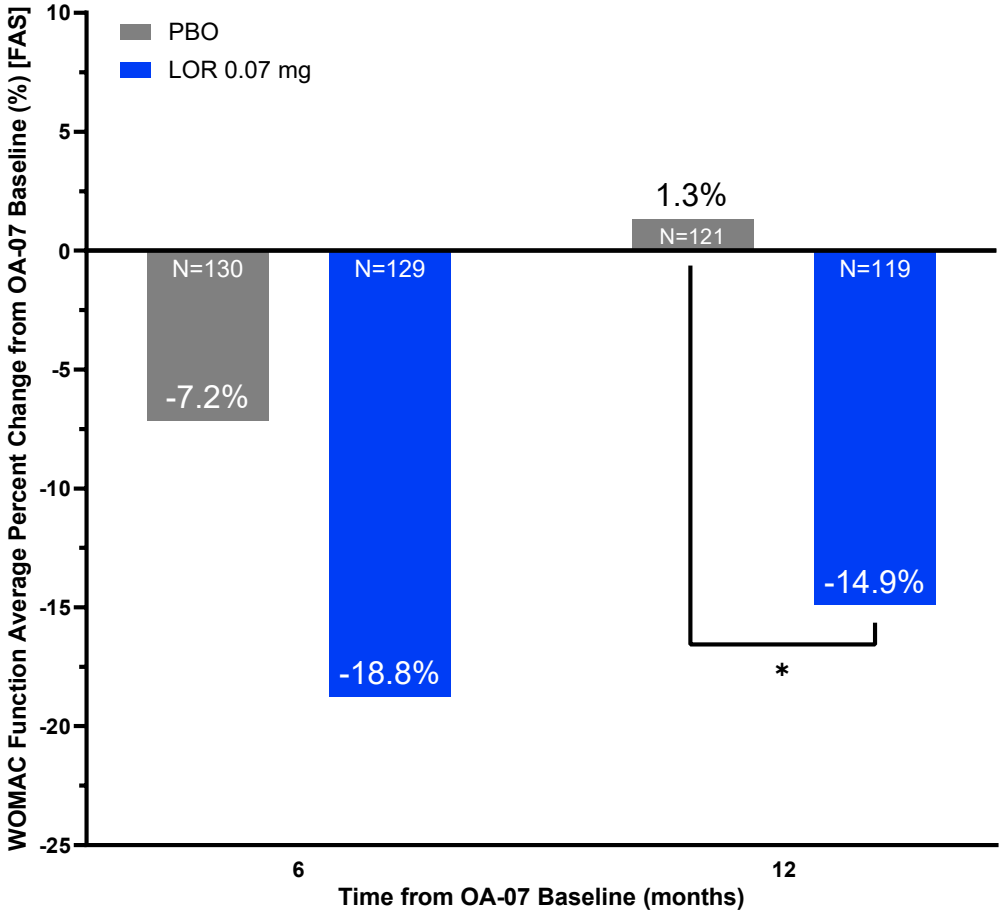
Results: WOMAC Function Change from Baseline



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 Osteoarthritis Index; **LOR**=lorecivivint; **PBO**=placebo

Results: WOMAC Function Change from Baseline (%)



Observed mean change repreesented as percent change shown.
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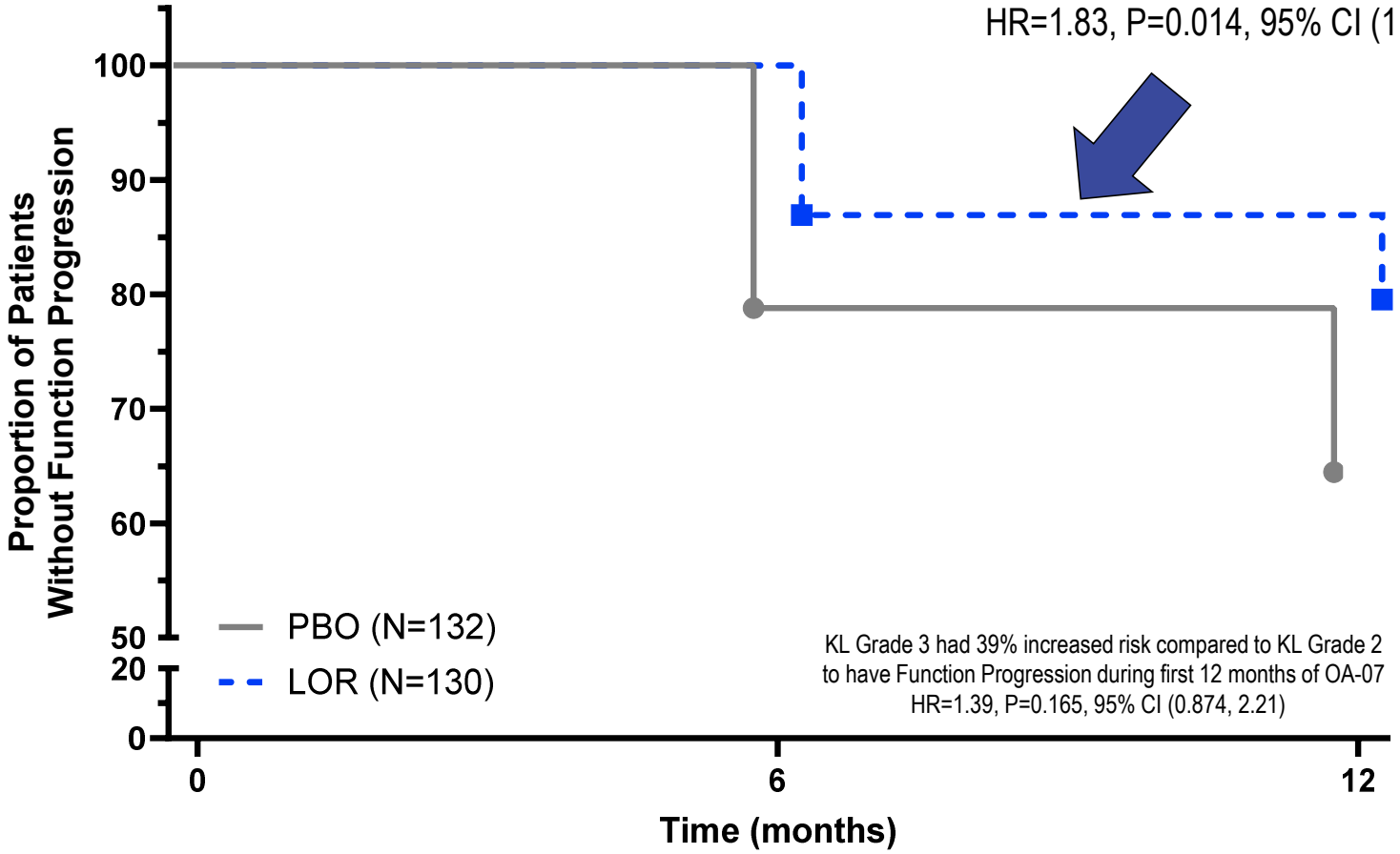
FAS=Full Analysis set; **WOMAC**=Western Ontario & McMaster Universities Osteoarthritis Index; **LOR**=lorecivivint; **PBO**=placebo

Results: LOR Significantly Lowered Function Progression Risk

Change in WOMAC Function [0-100] > 9 points

PBO had 83% increased risk compared to LOR
to have Function Progression during first 12 months of OA-07
HR=1.83, P=0.014, 95% CI (1.13, 2.96)



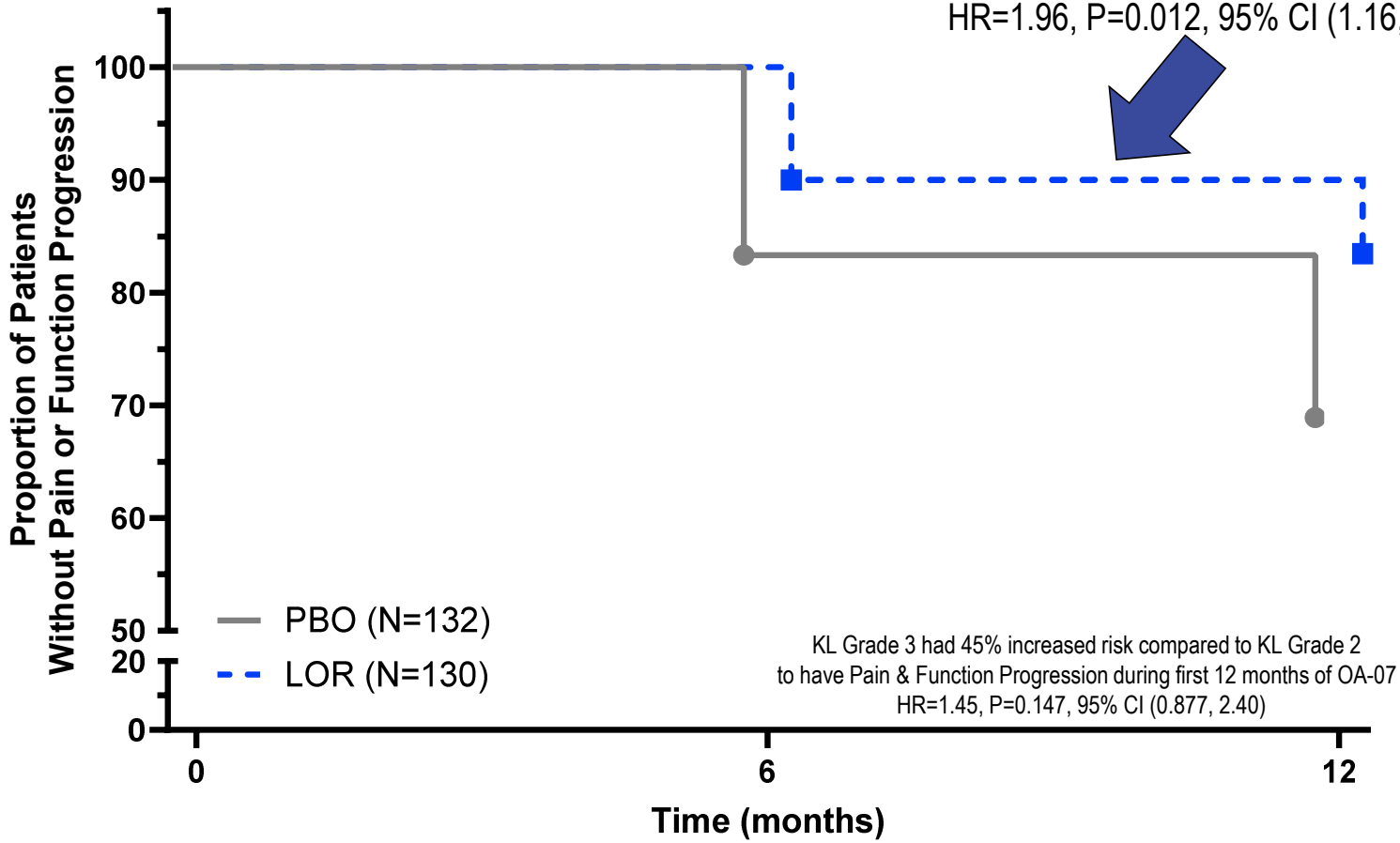
KL Grade 3 had 39% increased risk compared to KL Grade 2
to have Function Progression during first 12 months of OA-07
HR=1.39, P=0.165, 95% CI (0.874, 2.21)

WOMAC=Western Ontario & McMaster Universities Osteoarthritis Index; **LOR**=lorecivivint; **PBO**=placebo; **KL**=Kellgren-Lawrence; *Post-hoc Analysis*

Results: LOR Significantly Reduced Both Pain & Function Progression

Change in both WOMAC Pain ≥ 10 & WOMAC Function > 9

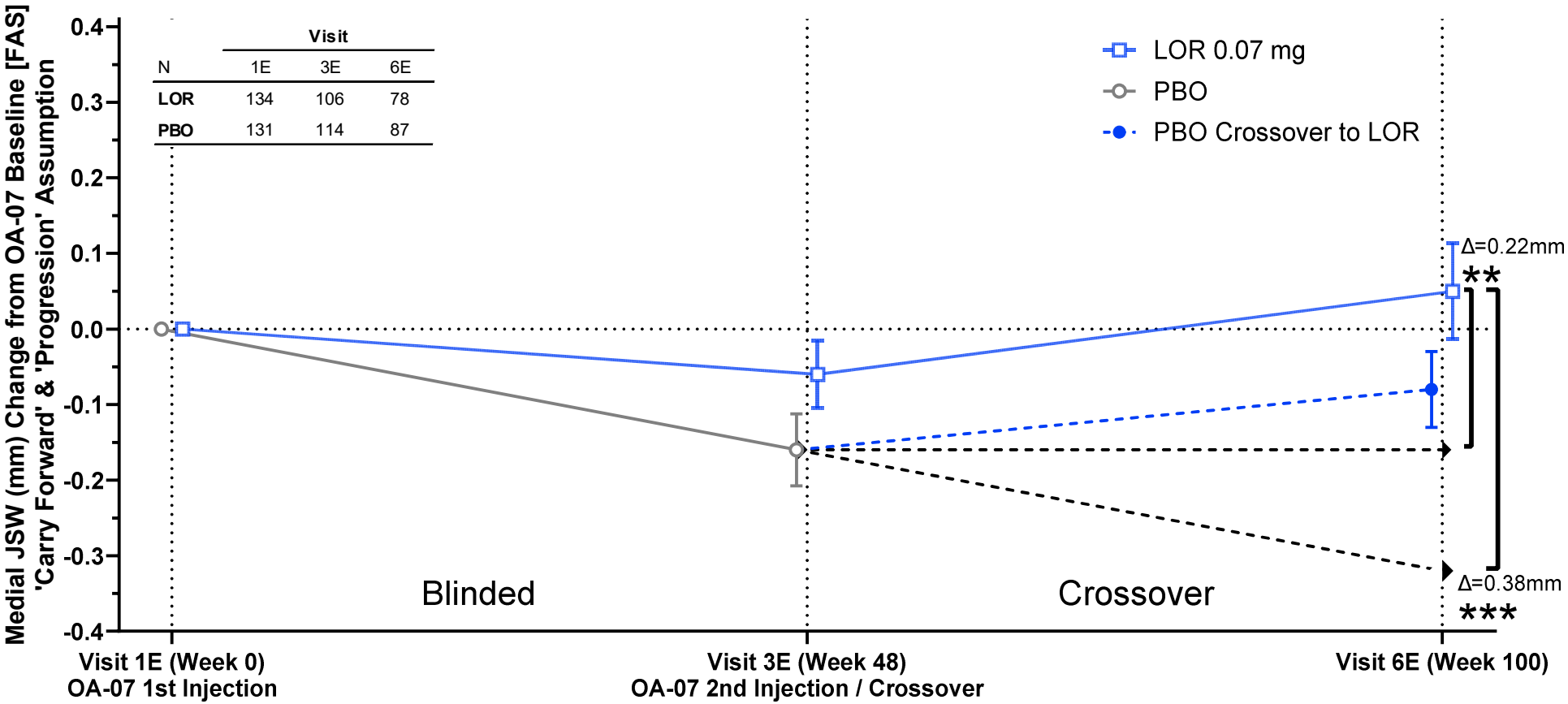
PBO had 96% increased risk compared to LOR
to have Pain & Function Progression during first 12 months of OA-07
HR=1.96, P=0.012, 95% CI (1.16, 3.33)



KL Grade 3 had 45% increased risk compared to KL Grade 2
to have Pain & Function Progression during first 12 months of OA-07
HR=1.45, P=0.147, 95% CI (0.877, 2.40)

WOMAC=Western Ontario & McMaster Universities Osteoarthritis Index; **LOR**=lorecivivint; **PBO**=placebo; **KL**=Kellgren-Lawrence; *Post-hoc Analysis*

Results: Structural Improvement



Observed mean ± standard error shown.
**P<0.01 ***P<0.001 LOR 0.07mg baseline-adjusted ANCOVA estimate tested against the PBO assumption.

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

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

Conclusions

- 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
  - Less progression of pain and function with LOR compared to PBO at 12 months
  - Structure was improved at 24 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

Results: 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..

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	2 (1.4%)	1 (0.7%)	2 (1.7%)	4 (3.6%)	2 (2.0%)	0 (0%)
Not Serious	42 (30.4%)	44 (31.9%)	26 (22.0%)	32 (29.1%)	10 (10.1%)	9 (10.6%)
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)