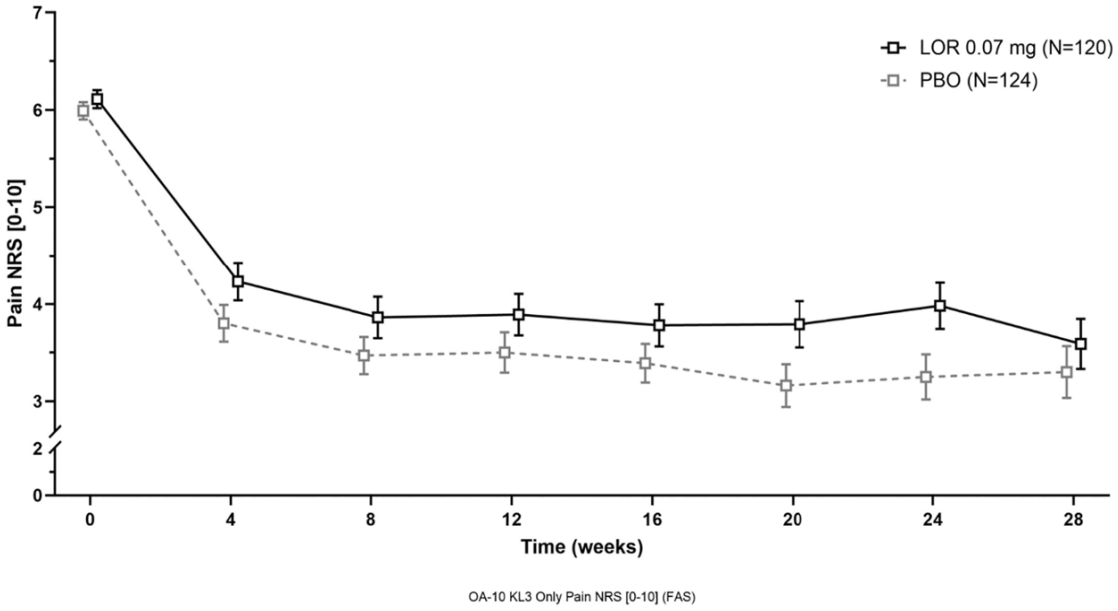
Supplementary Table S1. Baseline-adjusted ANCOVA for change in outcomes by KL Grade 2 (Full Analysis Set).

		Planned treatment						
		Placebo		Lorecivivint				
Parameter	Timepoint	n	Estimate (SE) {a}	n	Estimate (SE) {a}	Difference (SE) {b}	95% CI {c}	*p*-value {c}
Weekly Pain NRS (0-100)	Week 4	108	-1.62 (0.20)	96	-2.24 (0.21)	-0.62 (0.29)	(-1.20, -0.04)	0.036
	Week 12	102	-1.86 (0.22)	97	-2.31 (0.23)	-0.46 (0.32)	(-1.09, 0.17)	0.155
	Week 24	97	-2.02 (0.24)	88	-2.62 (0.26)	-0.61 (0.35)	(-1.31, 0.09)	0.089
WOMAC Function (0-100)	Week 4	109	-14.77 (2.00)	105	-19.46 (2.04)	-4.69 (2.86)	(-10.33, 0.96)	0.103
	Week 12	103	-18.91 (2.09)	105	-21.71 (2.07)	-2.80 (2.95)	(-8.62, 3.03)	0.345
	Week 24	101	-20.68 (2.17)	97	-24.09 (2.22)	-3.41 (3.11)	(-9.54, 2.73)	0.275
WOMAC Pain (0-100)	Week 4	109	-15.53 (1.95)	105	-20.25 (1.98)	-4.72 (2.79)	(-10.22, 0.78)	0.092
	Week 12	103	-19.31 (2.13)	105	-22.23 (2.11)	-2.92 (3.01)	(-8.86, 3.02)	0.333
	Week 24	101	-20.88 (2.18)	97	-23.82 (2.23)	-2.94 (3.12)	(-9.10, 3.22)	0.347
Patient Global (0-100)	Week 4	110	-16.91 (2.02)	105	-23.91 (2.06)	-7.00 (2.89)	(-12.69, -1.31)	0.016
	Week 12	108	-19.43 (2.21)	106	-24.16 (2.23)	-4.73 (3.14)	(-10.93, 1.46)	0.134
	Week 24	105	-20.19 (2.39)	97	-27.42 (2.48)	-7.23 (3.45)	(-14.03, -0.43)	0.037

KL: Kellgren-Lawrence; NRS: numeric rating scale; WOMAC: Western Ontario and McMaster Universities Arthritis Index; SE: standard error; CI: confidence interval; EOS: end of study.
{a} Least squares estimate is based on an ANCOVA model, adjusted for baseline value.
{b} Lorecivivint – placebo
{c} Unadjusted for multiplicity



Supplementary Fig. S1. Change from baseline in Pain NRS over time for KL Grade 3 patients.
KL: Kellgren and Lawrence (OA classification system); LOR: lorecivivint; NRS: numerical rating score; PBO: placebo; N: number.
Change from baseline in weekly average of daily Pain NRS (0-10) (means ± standard errors) shown.

Supplementary Table S2. Summary of outcomes and change from baseline by KL Grade 2 (Full Analysis Set).

			Planned treatment			
			Placebo		Lorecivivint	
Parameter	Timepoint	Statistic	Observed	Change from Baseline	Observed	Change from Baseline
Weekly Pain NRS [0-10]	Baseline	n	115	NA	111	NA
		Mean (SD)	6.09 (0.98)	NA	5.84 (0.91)	NA
	Week 4	n	108	108	96	96
		Mean (SD)	4.41 (2.07)	-1.67 (2.05)	3.71 (2.17)	-2.17 (2.27)
	Week 12	n	102	102	97	97
		Mean (SD)	4.17 (2.42)	-1.92 (2.46)	3.63 (2.09)	-2.24 (2.15)
	Week 24	n	97	97	88	88
		Mean (SD)	3.99 (2.58)	-2.08 (2.60)	3.31 (2.21)	-2.55 (2.31)
WOMAC Function [0-100]	Baseline	n	115	NA	110	NA
		Mean (SD)	59.65 (9.65)	NA	57.31 (9.27)	NA
	Week 4	n	109	109	106	105
		Mean (SD)	44.29 (21.40)	-15.05 (20.52)	38.09 (22.24)	-19.17 (21.50)
	Week 24	n	101	101	98	97
		Mean (SD)	38.17 (22.18)	-21.04 (21.75)	33.90 (22.23)	-23.71 (23.08)
WOMAC Pain [0-100]	Baseline	n	115	NA	110	NA
		Mean (SD)	57.98 (11.05)	NA	54.98 (10.14)	NA
	Week 4	n	109	109	106	105
		Mean (SD)	41.82 (21.21)	-16.07 (20.33)	35.25 (21.07)	-19.70 (20.88)
	Week 12	n	103	103	106	105
		Mean (SD)	37.75 (22.88)	-19.92 (22.06)	33.42 (21.41)	-21.64 (22.15)
	Week 24	n	101	101	98	97
		Mean (SD)	36.22 (23.41)	-21.31 (21.98)	31.98 (21.69)	-23.38 (22.64)
Patient Global [0-100]	Baseline	n	115	NA	109	NA
		Mean (SD)	62.96 (9.82)	NA	61.38 (10.23)	NA
	Week 4	n	110	110	107	105
		Mean (SD)	45.64 (21.53)	-17.36 (22.08)	37.57 (21.36)	-23.43 (22.14)
	Week 12	n	108	108	108	106
		Mean (SD)	42.87 (24.69)	-19.81 (26.30)	37.50 (21.23)	-23.77 (22.49)
	Week 24	n	105	105	99	97
		Mean (SD)	42.19 (25.46)	-20.48 (26.40)	34.44 (23.35)	-27.11 (25.16)
	Week 28 (EOS)	n	95	95	88	87
		Mean (SD)	39.26 (25.98)	-23.68 (26.54)	34.89 (24.31)	-26.32 (24.78)

KL: Kellgren-Lawrence; NRS: numeric rating scale; WOMAC: Western Ontario and McMaster Universities Arthritis Index; SD: standard deviation.

Supplementary Table S3. Reasons for screen failure.

Inclusion/exclusion criterion not met*	Screened n=1107 n (%)
I13 - WOMAC Function score of 68-136 for the target knee at baseline regardless of if the subject is on symptomatic oral treatment	135 (12.2%)
I11 - Daily OA knee pain diary average NRS intensity score ³ 4 and ≤ 8 in the target knee on the 11-point (0-10) NRS scale for the 7 days immediately preceding Day 1	99 (8.9%)
I12 - Daily OA knee pain diary average NRS intensity score < 4 in the non-target knee on the 11-point (0-10) NRS scale for the 7 days immediately preceding Day 1	59 (5.3%)
I17 - Full understanding of the requirements of the study and willingness to comply with all study visits and assessments	48 (4.3%)
I15 - Negative drug test for amphetamine, buprenorphine, cocaine, etc., except if any such drugs are clinically indicated and allowed by the protocol	47 (4.2%)
I08 - Widespread Pain Index (WPI) score of ≤ 4 and a Symptom Severity Question 2 score of ≤ 2 at the Screening Visit and Day 1	32 (2.9%)
I07 - Body mass index ≤ 35 kg/m² at the Screening Visit	28 (2.5%)
E28 - Hemoglobin A1c > 9 at the Screening Visit	27 (2.4%)
I09 - Pain NRS scores recorded for the target knee on at least 4 out of the 7 days immediately preceding Day 1	18 (1.6%)
E21 - Clinically significant abnormal screening hematology values, blood chemistry values, or urinalysis values as determined by the Investigator	14 (1.3%)
E15 - Use of centrally acting analgesics (refer to Appendix 2) within 12 weeks prior to Day 1	10 (0.9%)
E04A - Significant malalignment of anatomical axis of the target knee by radiograph within 24 weeks of the Screening Visit as assessed by independent central readers	9 (0.8%)
E22 - Any condition in the opinion of the Investigator constitutes a risk or contraindication for participation in study or that could interfere with study objectives, conduct, or evaluation	9 (0.8%)
E26 - Known active infections, *e.g.* urinary tract infection, upper respiratory infection, sinusitis, suspicion of intraarticular infection, hepatitis B or hepatitis C infection, infections that may compromise immune system such as human immunodeficiency virus at Day	19 (0.8%)
I10 - Pain NRS scores recorded for the nontarget knee on at least 4 out of the 7 days immediately preceding Day 1	7 (0.6%)
I14 - Willingness to use an electronic diary daily in the evening for the screening period and 28-week study duration	7 (0.6%)
E08 - IA injection in target knee w/ therapeutic aim incl., hyaluronic acid, platelet-rich plasma, and stem cell therapies w/in 26 weeks prior Day 1 or IA glucocorticoids w/in 12 weeks prior Day 1	6 (0.5%)
E16 - Use of anticonvulsants (refer to Appendix 2) within 12 weeks prior to Day 1	6 (0.5%)
E27 - Any chronic condition not well controlled or subjects with chronic condition who have not maintained stable therapeutic regimen of prescriptive therapy in opinion of Investigator	6 (0.5%)
E24 - Comorbid conditions that could affect study endpoint assessments of the target knee (*e.g.* rheumatoid or psoriatic arthritis, sys lupus erythematosus, gout or pseudogout, fibromyalgia)	5 (0.5%)
I02 - Ambulatory (single assistive devices such as canes allowed if needed less than 50% of the time, subjects requiring a walker are excluded)	4 (0.4%)
E05 - Partial or complete joint replacement in either knee	2 (0.2%)
E06 - Currently requires use of lower extremity prosthesis and/or a structural knee brace (*i.e.* a knee brace that contains hardware)	2 (0.2%)
E14 – Treatment with systemic glucocorticoids ³10 mg prednisone or equiv. per day within 4 weeks prior Day 1; or subjects on < 10 mg prednisone or equiv. per day not stable regimen at least 2 weeks prior Day 1	2 (0.2%)
E31 - Subjects who have a current or pending disability claim, workers' compensation, or litigation(s) that may compromise response to treatment	2 (0.2%)
I04A - Radiographic disease Stage 2 or 3 in target knee within 24 weeks of the Screening Visit according to the Kellgren-Lawrence grading of knee OA as assessed by independent central readers	2 (0.2%)
I16 - Subjects with depression or anxiety must be clin stable for at least 12 weeks prior to Screening Visit and if on treatment for depression or anxiety, be on at least 12 wks of stable therapy	2 (0.2%)
E02 - Women who are not post-menopausal or permanently surgically sterile who are sexually active and are not willing to use birth control during the study period	1 (0.1%)
E04 - Significant malalignment of anatomical axis of the target knee by radiograph within 12 weeks of the Screening Visit as assessed by independent central readers	1 (0.1%)
E07 - Any surgery (*e.g.* arthroscopy) in either knee within 26 weeks prior to Day 1	1 (0.1%)
E13 - Participation in clinical research trial w/ receipt of investigational product or experimental therapeutic procedure w/in 26 weeks prior to Screening, or planned participation in trial	1 (0.1%)
E17 - Subjects requiring the use of opioids > 1x per week within 12 weeks prior to Day 1	1 (0.1%)
E19 - Planned surgery scheduled during the study period, not including non-surgical invasive procedures conducted for a diagnostic or therapeutic purpose scheduled during the study period	1 (0.1%)
E20 - History of malignancy within the last 5 years, not including subjects with prior history of adequately treated *in situ* cervical cancer or basal or squamous cell skin cancer	1 (0.1%)
E25 - History of mania, bipolar disorder, psychotic disorder, schizophrenia, or schizoaffective disorder	1 (0.1%)
E30 - Any contraindications for an intraarticular injection in the target knee in the opinion of the Investigator	1 (0.1%)
I01 - Males and females between 40 and 80 years of age, inclusive, in general good health apart from their knee OA	1 (0.1%)
I06 - Primary source of pain throughout the body is due to OA in the target knee	1 (0.1%)
I18 - Subjects must have read and understood the Informed Consent Form, and must have signed and dated it prior to any study-related procedure being performed	1 (0.1%)

NRS: numeric rating scale; OA: osteoarthritis; WOMAC: Western Ontario and McMaster Universities Arthritis Index.
Screen Failure Reasons indexed by Inclusion [I] or Exclusion [E] criterion number; [A] denotes an inclusion/exclusion criterion that was changed due to a protocol amendment.