Novartis Clinical Trial Results

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

LRX712

Trial Indication(s)

Osteoarthritis

Protocol Number

CLRX712X2101

Protocol Title

A randomized, placebo controlled, subject and investigator blinded, first-in-human, single ascending dose study to evaluate the safety, tolerability, and pharmacokinetics after intraarticular injection of LRX712 into the knee of osteoarthritic patients.

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase I

Study Start/End Dates

20-Nov-2017 to 26-Mar-2019

Reason for Termination

Not applicable.

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Study Design/Methodology

This was a patient and investigator blinded, randomized, placebo-controlled, non confirmatory, first-in-human (FIH), Intra-articular (i.a.), Single ascending dose (SAD) study in OA patients.

Seven cohorts were planned for dose escalation from dose 1 to dose 2. Six patients in each cohort were randomized to receive either active LRX712 i.a. injection (4 patients) or placebo (2 patients).

Centers

1 center in 1 country: Netherlands

Objectives:

Primary objective

To evaluate safety and tolerability of LRX712 after a single intra-articular (i.a.) injection in osteoarthritic patients.

Secondary objective

To evaluate LRX712 and metabolite MAE344 pharmacokinetics in plasma.

Test Product, Dose, and Mode of Administration

LRX712 and placebo were supplied to the investigators at dose strengths of (25 mg/mL suspension for injection). The volume of the i.a. injection was fixed at 3 mL for all doses.

Dose 1=0.5 mg; Dose 2=2.5 mg; Dose 3=7.5 mg; Dose 4=15 mg; Dose 5=25 mg; Dose 6=40 mg; Dose 7 =75 mg

Statistical Methods

Statistical methods for safety parameters

The primary safety and tolerability variables were adverse events (CTC-AE), ECG parameters, 24 hour Holter monitoring, vital signs (body temperature, blood pressure, pulse rate), safety laboratory blood and urine samples (haematology, biochemistry, urinalysis).
All information obtained on adverse events were displayed by treatment and patient.
The number and percentage of patients with adverse events were tabulated by body system and preferred term with a breakdown by treatment. A patient with multiple adverse events within a body system was only counted once towards the total of this body system and treatment.
A 24 hour Holter monitoring data were collected, stored by the corresponding vendor for further analyses, if necessary.

Scatterplots of QTcF interval vs PK concentration and RR interval vs PK concentration were presented. These included Pearson's correlation coefficient along with the p-value, a regression line and the regression line equation.

Statistical methods for PK and biomarker parameters

Variables:

LRX712 and metabolite MAE344 concentrations were determined in plasma and synovial fluid using validated Liquid Chromatography with tandem mass spectrometry (LC-MS/MS) methods.

The following plasma PK parameters of LRX712 were determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (8.0): Cmax, Tmax, AUClast, AUCinf, %AUCinf, T1/2, Vz/F and CL/F from the plasma concentration-time data after single i.a., dose administration of LRX712. In addition, dose normalized parameters were calculated for Cmax, AUClast and AUCinf. Further, PK parameters of the metabolite MAE344 were calculated as appropriate.

The linear trapezoidal rule was used for AUC calculation. Regression analysis of the terminal plasma elimination phase for the determination of T1/2 included at least 3 data points after Cmax. If the adjusted R2 value of the regression analysis of the terminal phase was less than 0.75, no values were reported for T1/2, AUCinf, Vz/F and CL/F.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Male and female patients, 30 to 65 years of age inclusive, and in good health as determined by medical history, physical examination, vital signs, electrocardiogram, and laboratory tests at screening.
- At screening, and at baseline vital signs (systolic and diastolic blood pressure and pulse rate) will be assessed in the sitting position after the subject has rested for at least three minutes, and again (when required) after three minutes in the standing position as outlined in the SOM.

Sitting vital signs should be guided by the following ranges:

- body temperature between 35.0-37.5 °C
- systolic blood pressure 90-139 mm Hg
- diastolic blood pressure 50-89 mm Hg
- pulse rate, 40 - 90 bpm • Subjects must weigh at least 50 kg to participate in the study and must have a body mass index (BMI) within the range of 18 - 32 kg/m2. BMI = Body weight (kg) / [Height (m)]

Exclusion Criteria:

- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant.
- Pregnant or nursing (lactating) women

- Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or within 30 days, whichever is longer; or longer if required by local regulations
- A history of clinically significant ECG abnormalities, or any of the following ECG abnormalities at screening and baseline
  - PR > 200 msec
  - QRS complex > 120 msec
  - QTcF > 450 msec (males)
  - QTcF > 460 msec (females)
- Known family history or known presence of long QT syndrome

Participant Flow Table

Patient disposition - n (percent) of patients (All patients)

Epoch: *Screening

	LRX712 Dose 1 N=4 n (%)	LRX712 Dose 2 N=4 n (%)	LRX712 Dose 3 N=4 n (%)	LRX712 Dose 4 N=4 n (%)	LRX712 Dose 5 N=4 n (%)	LRX712 Dose 6 N=4 n (%)	LRX712 Dose 7 N=4 n (%)	Placebo i.a. N=14 n (%)	Total N=42 n (%)
Patients									
Completed	4 (100.0)	4 (100.0)	4 (100.0)	4 (100.0)	4 (100.0)	4 (100.0)	4 (100.0)	14 (100.0)	42 (100.0)

*Screen failures were not included in the trial database and hence, the patients Listing 16.2.4-1.2 contains enrolled patients only.
N = Number of patients entered the epoch

Patient disposition - n (percent) of patients (All patients)

Epoch: Treatment

	LRX712 Dose 1 N=4 n (%)	LRX712 Dose 2 N=4 n (%)	LRX712 Dose 3 N=4 n (%)	LRX712 Dose 4 N=4 n (%)	LRX712 Dose 5 N=4 n (%)	LRX712 Dose 6 N=4 n (%)	LRX712 Dose 7 N=4 n (%)	Placebo i.a. N=14 n (%)	Total N=42 n (%)
Patients									
Completed	4 (100.0)	4 (100.0)	4 (100.0)	4 (100.0)	4 (100.0)	4 (100.0)	4 (100.0)	14 (100.0)	42 (100.0)

N = Number of patients entered the epoch

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Baseline Characteristics

Patient demographics (Safety analysis set)-Part 1

		LRX712 Dose 1 N=4	LRX712 Dose 2 N=4	LRX712 Dose 3 N=4	LRX712 Dose 4 N=4	LRX712 Dose 5 N=4
Age (years)	Mean (SD)	58.5 (7.94)	59.3 (5.74)	50.0 (5.94)	57.5 (4.12)	60.5 (4.20)
	Q1	52.5	54.5	45.5	55.0	57.5
	Median	60.0	58.5	50.0	58.0	61.0
	Q3	64.5	64.0	54.5	60.0	63.5
	Range	[48, 66]	[54, 66]	[43, 57]	[52, 62]	[55, 65]
Sex - n (%)	Male	2 (50.0)	0 (0.0)	1 (25.0)	1 (25.0)	2 (50.0)
	Female	2 (50.0)	4 (100.0)	3 (75.0)	3 (75.0)	2 (50.0)
Race - n (%)	White	4 (100.0)	3 (75.0)	4 (100.0)	4 (100.0)	3 (75.0)
	Other	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	1 (25.0)
Ethnicity - n (%)	Not Hispanic or Latino	4 (100.0)	4 (100.0)	4 (100.0)	4 (100.0)	4 (100.0)
Weight (kg)	Mean (SD)	80.95 (12.269)	78.25 (5.292)	80.78 (25.925)	78.82 (10.392)	88.10 (13.213)
	Q1	71.45	74.55	59.25	71.80	78.85
	Median	83.45	76.75	77.85	75.85	89.45
	Q3	90.45	81.95	102.30	85.85	97.35
	Range	[64.9, 92.0]	[73.8, 85.7]	[56.5, 110.9]	[70.0, 93.6]	[70.9, 102.6]
Height (cm)	Mean (SD)	173.88 (3.931)	167.80 (4.357)	175.95 (9.669)	171.20 (4.069)	173.68 (8.694)
	Q1	171.15	164.75	169.85	167.90	167.55
	Median	173.20	166.65	176.60	170.75	173.85
	Q3	176.60	170.85	182.05	174.50	179.80
	Range	[169.9, 179.2]	[164.0, 173.9]	[163.5, 187.1]	[167.2, 176.1]	[163.0, 184.0]
Body Mass Index (kg/m2)	Mean (SD)	26.68 (3.291)	27.75 (0.404)	25.63 (5.913)	26.85 (2.894)	29.13 (3.003)
	Q1	24.10	27.45	20.55	24.65	26.95
	Median	27.15	27.65	25.50	26.90	28.25
	Q3	29.25	28.05	30.70	29.05	31.30
	Range	[22.5, 29.9]	[27.4, 28.3]	[20.0, 31.5]	[23.4, 30.2]	[26.7, 33.3]

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Patient demographics (Safety analysis set)-Part 2

		LRX712 Dose 6 N=4	LRX712 Dose 7 N=4	Placebo i.a. N=14	Total N=42
Age (years)	Mean (SD)	58.8 (11.90)	58.8 (4.57)	56.1 (8.32)	57.1 (7.32)
	Q1	52.0	55.0	54.0	54.0
	Median	64.0	58.5	57.0	57.5
	Q3	65.5	62.5	62.0	62.0
	Range	[41, 66]	[54, 64]	[30, 64]	[30, 66]
Sex - n (%)	Male	2 (50.0)	2 (50.0)	3 (21.4)	13 (31.0)
	Female	2 (50.0)	2 (50.0)	11 (78.6)	29 (69.0)
Race - n (%)	White	3 (75.0)	4 (100.0)	14 (100.0)	39 (92.9)
	Other	1 (25.0)	0 (0.0)	0 (0.0)	3 (7.1)
Ethnicity - n (%)	Not Hispanic or Latino	4 (100.0)	4 (100.0)	14 (100.0)	42 (100.0)
Weight (kg)	Mean (SD)	75.43 (10.345)	89.93 (20.307)	73.79 (10.838)	79.10 (13.753)
	Q1	68.50	72.95	68.00	70.00
	Median	75.75	86.70	74.20	75.60
	Q3	82.35	106.90	77.10	87.70
	Range	[62.5, 87.7]	[72.9, 113.4]	[55.2, 98.9]	[55.2, 113.4]
Height (cm)	Mean (SD)	168.68 (6.028)	177.55 (10.615)	173.48 (10.149)	172.94 (8.216)
	Q1	164.95	168.60	167.80	167.80
	Median	169.45	177.10	171.50	172.20
	Q3	172.40	186.50	177.70	177.00
	Range	[160.6, 175.2]	[167.0, 189.0]	[161.4, 200.8]	[160.6, 200.8]
Body Mass Index (kg/m2)	Mean (SD)	26.48 (2.960)	28.18 (3.050)	24.51 (3.001)	26.33 (3.364)
	Q1	24.25	25.65	22.80	23.50
	Median	25.60	27.90	24.00	26.65
	Q3	28.70	30.70	26.60	29.30
	Range	[24.2, 30.5]	[25.2, 31.7]	[19.6, 30.3]	[19.6, 33.3]

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Primary Outcome Results

Refer to Safety Result section for primary outcome result.

Secondary Outcome Results

Summary statistics of plasma PK parameter values of LRX712

PK parameter (unit)	LRX712 Dose 1 N=4	LRX712 Dose 2 N=4	LRX712 Dose 3 N=4	LRX712 Dose 4 N=4	LRX712 Dose 5 N=4	LRX712 Dose 6 N=4	LRX712 Dose 7 N=4
Cmax (ng/mL)	0.413 ± 0.329 (79.8)	2.27 ± 1.77 (78.1)	8.79 ± 6.24 (71.0)	3.85 ± 4.13 (107.4)	18.0 ± 4.25 (23.7)	17.6 ± 9.50 (54.1)	19.3 ± 11.7 (60.9)
Tmax (hr) #	4.00 (4.00-4.00)	6.49 (4.00-24.0)	4.00 (4.00-4.00)	24.0 (3.98-24.0)	18.1 (8.00-24.3)	24.0 (8.00-24.0)	14.0 (4.00-24.0)
AUClast (hr*ng/mL)	7.37 ± 3.87 (52.5)	67.5 ± 34.5 (51.1)	172 ± 116 (67.7)	335 ± 78.8 (23.5)	856 ± 282 (32.9)	1100 ± 393 (35.6)	1420 ± 840 (59.3)
AUCinf (hr*ng/mL)	8.32 ± 3.82 (45.9)	69.4 ± 34.4 (49.5)	174 ± 116 (66.4)	405 ± 111 (27.4)	858 ± 281 (32.7)	1270 ± 585 (46.1)	1650 ± 1090 (66.1)
T1/2 (hr)	23.2 ± 2.58 (11.1)	42.4 ± 31.4 (74.2)	27.4 ± 3.36 (12.3)	239 ± 160 (66.8)	32.8 ± 7.15 (21.8)	48.7 ± 31.1 (64.0)	179 ± 162 (90.4)
Vz/F (L)	2430 ± 1280 (52.5)	2750 ± 2290 (83.4)	2210 ± 1100 (49.6)	12100 ± 7960 (65.6)	1530 ± 735 (48.1)	2110 ± 443 (21.0)	15000 ± 18100 (120.6)
CL/F (L/hr)	70.3 ± 30.9 (43.9)	46.7 ± 30.2 (64.7)	58.5 ± 33.8 (57.8)	39.1 ± 9.98 (25.5)	31.5 ± 9.88 (31.3)	35.3 ± 16.3 (46.1)	61.1 ± 33.4 (54.7)

Statistics are Mean ± SD (CV%)

CV% = Coefficient of variation (%) = sd/mean*100

For Tmax, statistics are Median (Min-Max)

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Summary statistics of plasma PK parameter values of MAE344

PK parameter (unit)	LRX712 Dose 1 N=4	LRX712 Dose 2 N=4	LRX712 Dose 3 N=4	LRX712 Dose 4 N=4	LRX712 Dose 5 N=4	LRX712 Dose 6 N=4	LRX712 Dose 7 N=4
Cmax (ng/mL)	2.43 ± 1.65 (68.0)	10.2 ± 5.55 (54.2)	47.6 ± 20.8 (43.8)	45.4 ± 51.9 (114.4)	148 ± 25.6 (17.3)	199 ± 122 (61.1)	161 ± 85.9 (53.5)
Tmax (hr) #	24.0 (8.00-24.1)	30.0 (8.00-36.0)	24.0 (12.0-24.0)	48.0 (24.0-54.0)	24.2 (24.0-30.0)	24.0 (24.0-48.0)	36.0 (24.0-72.0)
AUClast (hr*ng/mL)	137 ± 58.0 (42.4)	767 ± 359 (46.8)	2950 ± 1390 (47.2)	5550 ± 826 (14.9)	10600 ± 1950 (18.3)	16900 ± 5750 (33.9)	21000 ± 11700 (55.7)
AUCinf (hr*ng/mL)	147 ± 61.5 (41.9)	791 ± 428 (54.1)	2960 ± 1390 (47.0)	6790 ± 1440 (21.2)	10600 ± 1950 (18.4)	21300 ± 2650 (12.5)	23900 ± 14500 (60.8)
T1/2 (hr)	37.4 ± 10.9 (29.0)	29.6 ± 3.08 (10.4)	33.3 ± 1.08 (3.2)	245 ± 155 (63.3)	37.6 ± 9.14 (24.3)	46.0 ± 21.1 (45.9)	159 ± 136 (85.2)

Statistics are Mean ± SD (CV%)
CV% = Coefficient of variation (%) = sd/mean*100
For Tmax, statistics are Median (Min-Max)

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Safety Results

Incidence of AEs by primary system organ class - n (percent) of patients (Safety analysis set)

Primary system organ class	LRX712 Dose 1 N=4 n (%)	LRX712 Dose 2 N=4 n (%)	LRX712 Dose 3 N=4 n (%)	LRX712 Dose 4 N=4 n (%)	LRX712 Dose 5 N=4 n (%)	LRX712 Dose 6 N=4 n (%)	LRX712 Dose 7 N=4 n (%)	Placebo i.a. N=14 n (%)	Total N=42 n (%)
Number of patients with at least one AE	4 (100.0)	4 (100.0)	4 (100.0)	3 (75.0)	4 (100.0)	4 (100.0)	4 (100.0)	7 (50.0)	34 (81.0)
General disorders and administration site conditions	2 (50.0)	3 (75.0)	2 (50.0)	2 (50.0)	2 (50.0)	3 (75.0)	4 (100.0)	2 (14.3)	20 (47.6)
Musculoskeletal and connective tissue disorders	1 (25.0)	1 (25.0)	1 (25.0)	1 (25.0)	4 (100.0)	0 (0.0)	2 (50.0)	3 (21.4)	13 (31.0)
Nervous system disorders	1 (25.0)	2 (50.0)	1 (25.0)	1 (25.0)	1 (25.0)	2 (50.0)	1 (25.0)	3 (21.4)	12 (28.6)
Vascular disorders	0 (0.0)	1 (25.0)	1 (25.0)	0 (0.0)	2 (50.0)	1 (25.0)	0 (0.0)	2 (14.3)	7 (16.7)
Gastrointestinal disorders	0 (0.0)	2 (50.0)	1 (25.0)	1 (25.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (11.9)
Skin and subcutaneous tissue disorders	1 (25.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (25.0)	0 (0.0)	2 (14.3)	5 (11.9)
Infections and infestations	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	1 (25.0)	1 (25.0)	1 (7.1)	4 (9.5)
Cardiac disorders	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	2 (4.8)
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.8)
Respiratory, thoracic and mediastinal disorders	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	2 (4.8)
Investigations	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	1 (2.4)
Psychiatric disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	1 (2.4)

A patient with multiple AEs is counted only once in the 'at least one AE' row.

A patient with multiple AEs within a primary system organ class is counted only once for that system organ class treatment arranged in descending order of frequency (in total group) and alphabetically by system organ class

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Incidence of AEs by preferred term - n (percent) of patients (Safety analysis set)

Preferred term	LRX712 Dose 1 N=4 n (%)	LRX712 Dose 2 N=4 n (%)	LRX712 Dose 3 N=4 n (%)	LRX712 Dose 4 N=4 n (%)	LRX712 Dose 5 N=4 n (%)	LRX712 Dose 6 N=4 n (%)	LRX712 Dose 7 N=4 n (%)	Placebo i.a. N=14 n (%)	Total N=42 n (%)
Number of patients with at least one AE	4 (100.0)	4 (100.0)	4 (100.0)	3 (75.0)	4 (100.0)	4 (100.0)	4 (100.0)	7 (50.0)	34 (81.0)
Injection site pain	0 (0.0)	3 (75.0)	1 (25.0)	0 (0.0)	2 (50.0)	3 (75.0)	0 (0.0)	1 (7.1)	10 (23.8)
Back pain	1 (25.0)	0 (0.0)	1 (25.0)	0 (0.0)	2 (50.0)	0 (0.0)	2 (50.0)	0 (0.0)	6 (14.3)
Headache	0 (0.0)	1 (25.0)	1 (25.0)	1 (25.0)	0 (0.0)	1 (25.0)	1 (25.0)	1 (7.1)	6 (14.3)
Injection site joint movement impairment	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	2 (50.0)	2 (50.0)	0 (0.0)	5 (11.9)
Injection site swelling	0 (0.0)	1 (25.0)	1 (25.0)	0 (0.0)	0 (0.0)	2 (50.0)	0 (0.0)	1 (7.1)	5 (11.9)
Arthralgia	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	1 (25.0)	0 (0.0)	0 (0.0)	1 (7.1)	3 (7.1)
Hypertension	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (25.0)	1 (25.0)	0 (0.0)	0 (0.0)	3 (7.1)
Injection site joint pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (75.0)	0 (0.0)	3 (7.1)
Musculoskeletal stiffness	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	1 (7.1)	3 (7.1)
Nausea	0 (0.0)	1 (25.0)	0 (0.0)	1 (25.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (7.1)
Erythema	1 (25.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.8)
Hot flush	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	2 (4.8)
Influenza like illness	2 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.8)
Injection site discomfort	1 (25.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.8)
Injection site reaction	1 (25.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.8)
Injection site warmth	2 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.8)
Nasopharyngitis	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	2 (4.8)
Sciatica	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	2 (4.8)
Skin irritation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (7.1)	2 (4.8)
Somnolence	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	1 (7.1)	2 (4.8)
Urinary tract infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	1 (7.1)	2 (4.8)
Abdominal pain upper	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)
Bleeding varicose vein	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)
Breath sounds abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	1 (2.4)
Chills	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (2.4)

Cough	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)
Dermatitis atopic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	1 (2.4)
Diarrhoea	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)
Dizziness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	1 (2.4)
Dysgeusia	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)
Fatigue	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)
Feeling cold	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (2.4)
Gastritis	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)
Haematoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	1 (2.4)
Hyperventilation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (2.4)
Injection site joint discomfort	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (2.4)
Injection site joint swelling	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (2.4)
Injection site movement impairment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	1 (2.4)
Injection site paraesthesia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	1 (2.4)
Insomnia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	1 (2.4)
Joint noise	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)
Ligament sprain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)
Myalgia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	1 (2.4)
Osteoarthritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)
Palpitations	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)
Skin abrasion	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)
Tachycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	1 (2.4)

A patient with multiple AEs is counted only once in the 'at least one AE' row

A patient with multiple AEs with the same preferred term is counted only once for that preferred term & treatment Arranged in descending order of frequency (in total group) and alphabetically by preferred term

Serious Adverse Events and Death

No deaths or serious adverse events were reported in the study.

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Conclusion:

The results of this first-in-human study indicated that LRX712 has a safety, tolerability and PK profile that supports further development including exploration of risk-benefit in the dose range most likely to be efficacious based on preclinical data. These clinical data suggest that intra-articular injection of LRX712 into the knee can be performed safely in patients with knee OA.

Date of Clinical Trial Report

20-Jan-2020