Sponsor

Novartis

Generic Drug Name

Lumiracoxib

Therapeutic Area of Trial

Osteoarthritis

Approved Indication

Registered indication worldwide (varies by country):

- Symptomatic treatment of osteoarthritis (OA)
- Treatment of acute pain
- Treatment of primary dysmenorrhea
- Treatment of acute gout

Study Number

CCOX189A2367

Title

A 13-week, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel group trial of lumiracoxib (COX189) 100 mg o.d. in patients with primary hip osteoarthritis using celecoxib (200 mg o.d.) as a positive control

Phase of Development

Phase III

Study Start/End Dates

15-Nov-2004 to 19-Oct-2006

Study Design/Methodology

This was a 13-week, randomized, multicenter, double-blind, double-dummy, placebo-controlled, parallel group study. Eligible patients were randomized in a 1:1:1 ratio to receive lumiracoxib 100 mg, celecoxib 200 mg or matching placebo administered orally once daily.

Centres

162 centers in 5 countries: Canada (42), United States (71), Germany (30), Italy (12), and United Kingdom (7).

Publication

Ongoing

Objectives

Primary objective(s)

To compare the efficacy of lumiracoxib in primary hip osteoarthritis to placebo with respect to the pain sub-scale of the Western Ontario and McMaster Universities Osteoarthritis Index Likert version 3.1 (WOMAC™ 3.1 LK) questionnaire, the difficulty performing daily activities (DPDA) sub-scale of the WOMAC™ 3.1 LK questionnaire and patient's global assessment of disease activity on a 100 mm visual analog scale (VAS) after 13 weeks of treatment

Secondary objective(s)

- To assess the safety and tolerability of lumiracoxib 100 mg o.d. in comparison to placebo and celecoxib 200 mg o.d.
- To assess the efficacy of lumiracoxib 100 mg o.d. as compared to placebo, with celecoxib 200 mg o.d. as a positive control, using the following variables: WOMAC™ 3.1 LK sub-scale and total scores by visit, overall OA pain intensity, physician's global assessment of disease activity by visit and patient's global assessment of disease activity by visit.

Test Product (s), Dose(s), and Mode(s) of Administration

Oral tablets of lumiracoxib 100 mg taken once a day in the morning.

Reference Product(s), Dose(s), and Mode(s) of Administration

Oral tablets of celecoxib 200 mg or placebo taken once a day in the morning.

Criteria for Evaluation

Primary variables

The three joint primary efficacy variables were:

- WOMAC™ pain sub-scale score at 13 weeks
- Patient's global assessment of disease activity (0-100 mm VAS) at 13 weeks
- WOMAC™ DPDA sub-scale score at 13 weeks

Secondary variables

- WOMAC™ 3.1 LK sub-scale scores (pain, DPDA, and stiffness) and total score by visit
- Patient's global assessment of disease activity using a 0-100 mm VAS by visit
- Physician's global assessment of disease activity using a 0-100 mm VAS by visit
- Overall OA pain intensity in the target hip using a 0-100 mm VAS by visit

Safety and tolerability

Safety assessments consisted of monitoring and recording all adverse events, serious adverse events (with their severity and relationship to study drug), and pregnancies, monitoring of significant liver events, gastrointestinal perforations, ulcers and bleeding, serious cardiovascular and cerebrovascular events, hematology, blood chemistry and urine and regular assessments of vital signs and physical condition.

Pharmacology

No assessments were performed.

Other

Not applicable.

Statistical Methods

All data from all study centers were combined, summarized and analyzed. Demographic and background characteristics were summarized. The confirmatory analysis of the primary variables was an analysis of covariance allowing for treatment, baseline value of the primary variable and center as explanatory variables. Using the least square means obtained from the primary analysis model, all between-treatment pair-wise contrasts and their 95% confidence intervals were calculated. The assessment of safety was based mainly on the occurrence of AEs and laboratory abnormalities. AEs were summarized by presenting the number and percentage of patients having an AE, having an AE in each body system, by severity, and by relationship to study medication. Laboratory data were listed; notable (outside pre-determined ranges) and abnormal (outside normal ranges) laboratory values were summarized. Data on vital signs were listed and notable values flagged. No interim analyses were performed.

Study Population: Inclusion/Exclusion Criteria and Demographics

The patients were recruited into the study if they:

- were male or female outpatients 40 years of age or older
- had the highest pain intensity occurring in the target hip joint, relative to other OA joints (including the contralateral hip).
- had a diagnosis of primary hip osteoarthritis which meets the American College of Rheumatology (ACR) criteria and had symptoms present for at least 3 months prior to screening.
- had taken NSAIDS or simple analgesic therapy at least 50% of the time in the previous month (i.e. for 15 or more days (either successive or not) in the past 30 days) and who in the opinion of the investigator would have required NSAID therapy for at least 13 weeks.
- had sedentary pain for at least 2 days of the week and non-sedentary pain for at least 50% of the days in the previous month (i.e. for 15 or more days (either successive or not) in the past 30 days).
- presented at Baseline (Visit 2) with an OA pain intensity of at least 40 mm (0-100 mm VAS) in the target hip during the last 24 hours, and an increase in OA pain intensity since the screening visit of ≥20% and ≥10 mm. Patients who reached 100 mm before achieving a 20% increase were eligible as long as the increase was at least 10 mm.
- were women who were:
  - surgically sterile (tubal ligation or hysterectomy), or
  - post-menopausal for at least 12 months with FSH > 40 IU/L, or
  - using an acceptable form of birth control.
- were fluent in a language in which scales, questions and/or questionnaires were printed and available at the site.
- had signed a written informed consent before any trial procedure was performed.

The patients were excluded from the study if they:

- had OA pain intensity of the knee(s) ≥ 30 mm (0-100 mm VAS) at screening
- had symptomatic osteoarthritis of the contralateral hip or spine that may, in the investigator's opinion, interfere with assessment of the target hip joint
- had open knee/hip surgery within the last year, or observational arthroscopy, arthroscopic surgery or lavage within the last 180 days (in the knee or hip)
- had complete, even if focal, loss of articular cartilage on weight-bearing x-ray of the target joint
- had primary fibromyalgia, rheumatoid arthritis, systemic lupus erythematosus, or other inflammatory joint disease, adult juvenile chronic arthritis, sarcoidosis, or symptomatic trochanteric bursitis of the target joint

Number of Subjects

	Lumiracoxib 100 mg o.d.	**Celecoxib 200 mg o.d.**	**Placebo**
Planned N	400	400	400
Randomised n	427	419	416
Intent-to-treat population (ITT) n (%)	427 (100.0)	419 (100.0)	416 (100.0)
Completed n (%)	337 (78.9)	327 (78.0)	287 (69.0)
Withdrawn n (%)	90 (21.1)	92 (22.0)	129 (31.0)
Withdrawn due to adverse events n (%)	22 (5.2)	22 (5.3)	18 (4.3)
Withdrawn due to lack of efficacy n (%)	37 (8.7)	32 (7.6)	80 (19.2)
Withdrawn for other reasons n (%)	31 (7.2)	38 (9.1)	31 (7.5)

Demographic and Background Characteristics

	Lumiracoxib 100 mg o.d.	**Celecoxib 200 mg o.d.**	**Placebo**
N (ITT)	427	419	416
Females : males	269:158	257:162	252:164
Mean age, years (SD)	61.7 (10.27)	61.7 (9.72)	61.4 (10.06)
Mean weight, kg (SD)	82.2 (19.06)	85.4 (18.12)	83.4 (18.75)
Race			
White n (%)	409 (95.8)	389 (92.8)	386 (92.8)
Black n (%)	14 (3.3)	17 (4.1)	18 (4.3)
Asian n (%)	1 (0.2)	5 (1.2)	2 (0.5)
Hispanic n (%)	3 (0.7)	6 (1.4)	10 (2.4)
Other n (%)	0 (0.0)	2 (0.5)	0 (0.0)
Characteristics relevant to study population			
Mean OA pain, VAS in mm [SD]	71.0 [14.10]	70.5 [15.46]	70.4 [15.37]
Mean Disease duration, years [SD]	4.2 [5.31]	3.7 [5.37]	3.8 [4.98]
Regular NSAID use n (%)			
No	1 (0.2)	0 (0.0)	0 (0.0)
Yes	426 (99.8)	419 (100.0)	416 (100.0)

Primary Objective Result(s)

WOMAC (pain and DPDA sub-scale scores) and patient's global assessment of disease activity after 13 week treatment (ITT population, LOCF)

Treatment Group	N	Least Square Mean	Contrast	Estimated Difference	95% CI of Difference	p-value[1]
WOMAC pain sub-scale score after 13 weeks treatment						
Lumiracoxib 100mg o.d.	424	7.17	LUM – CEL	0.08	-0.44, 0.60	0.766
			LUM – Placebo	-1.12	-1.63, -0.60	<0.001*
Celecoxib 200mg o.d.	418	7.09	CEL – Placebo	-1.20	-1.72, -0.67	<0.001*
Placebo	416	8.28				
Patient's global assessment of disease activity (VAS mm) after 13 weeks treatment						
Lumiracoxib 100mg o.d.	427	37.63	LUM – CEL	0.15	-3.10, 3.39	0.929
			LUM – Placebo	-8.59	-11.84, -5.33	<0.001*
Celecoxib 200mg o.d.	419	37.48	CEL – Placebo	-8.73	-12.01, -5.46	<0.001*
Placebo	416	46.22				
WOMAC DPDA sub-scale score after 13 weeks treatment						
Lumiracoxib 100mg o.d.	424	26.08	LUM – CEL	0.34	-1.33, 2.01	0.690
			LUM – Placebo	-3.58	-5.24, -1.91	<0.001*
Celecoxib 200mg o.d.	417	25.74	CEL – Placebo	-3.92	-5.59, -2.24	<0.001*
Placebo	416	29.65				

LUM = lumiracoxib 100 mg o.d.; CEL = celecoxib 200 mg o.d.
[1] ANCOVA with center, treatment, and corresponding baseline value. Contrasts tested at the 5% significance level. *p<0.05; p-values not adjusted for multiplicity

Secondary Objective Result(s)

WOMAC (Pain sub-scale score) by visit (ITT population, LOCF)

	Lumiracoxib 100mg o.d. N=427	Celecoxib 200mg o.d. N=419	Placebo N=416
Baseline			
n	424	418	416
Mean	10.8	10.8	10.6
Visit 3 (Week 4)			
n	424	418	416
Mean	7.9***	7.9***	8.9
Mean change	-2.9	-3.0	-1.7
Visit 4 (Week 8)			
n	424	418	416
Mean	7.4***	7.3***	8.6
Mean change	-3.4	-3.5	-2.0
Visit 5 (Week 13)			
n	424	418	416
Mean	7.3***	7.2***	8.4
Mean change	-3.4	-3.6	-2.2

Symbols: comparison with placebo, ANCOVA, *p<0.05, **p<0.01, ***p<0.001; p-values not adjusted for multiplicity.
Note: Change of pain rating is with respect to the baseline value.
Only those patients with both a baseline and post-treatment measurement are included.

WOMAC (DPDA sub-scale score) by visit (ITT population, LOCF)

	Lumiracoxib 100mg o.d. N=427	Celecoxib 200mg o.d. N=419	Placebo N=416
Baseline			
n	424	417	416
Mean	37.0	37.2	37.2
Visit 3 (Week 4)			
n	424	417	416
Mean	28.1***	28.2***	32.0
Mean change	-8.9	-9.0	-5.2
Visit 4 (Week 8)			
n	424	417	416
Mean	26.2***	26.6***	31.4
Mean change	-10.8	-10.6	-5.8
Visit 5 (Week 13)			
n	424	417	416
Mean	26.6***	26.3***	30.4
Mean change	-10.4	-10.9	-6.8

Symbols: comparison with placebo, ANCOVA, *p<0.05, **p<0.01, ***p<0.001; p-values not adjusted for multiplicity.
Note: Change of pain rating is with respect to the baseline value.
Only those patients with both a baseline and post-treatment measurement are included.

WOMAC (Stiffness sub-scale score) by visit (ITT population, LOCF)

	Lumiracoxib 100mg o.d. N=427	Celecoxib 200mg o.d. N=419	Placebo N=416
Baseline			
n	427	419	416
Mean	4.6	4.6	4.5
Visit 3 (Week 4)			
n	427	419	416
Mean	3.5***	3.5***	3.9
Mean change	-1.2	-1.1	-0.6
Visit 4 (Week 8)			
n	427	419	416
Mean	3.3***	3.3***	3.9
Mean change	-1.3	-1.3	-0.7
Visit 5 (Week 13)			
n	427	419	416
Mean	3.3***	3.3***	3.8
Mean change	-1.3	-1.3	-0.8

Symbols: comparison with placebo, ANCOVA, *p<0.05, **p<0.01, ***p<0.001; p-values not adjusted for multiplicity.
Note: Change of pain rating is with respect to the baseline value.
Only those patients with both a baseline and post-treatment measurement are included.

WOMAC (Total score) by visit (ITT population, LOCF)

	Lumiracoxib 100mg o.d. N=427	Celecoxib 200mg o.d. N=419	Placebo N=416
Baseline			
n	427	419	416
Mean	52.4	52.7	52.4
Visit 3 (Week 4)			
n	422	416	416
Mean	39.4***	39.6***	44.8
Mean change	-13.0	-13.1	-7.6
Visit 4 (Week 8)			
n	422	416	416
Mean	36.9***	37.3***	43.9
Mean change	-15.5	-15.4	-8.4
Visit 5 (Week 13)			
n	422	416	416
Mean	37.2***	36.9***	42.5
Mean change	-15.2	-15.8	-9.8

Symbols: comparison with placebo, ANCOVA, *p<0.05, **p<0.01, ***p<0.001; p-values not adjusted for multiplicity.
Note: Change of pain rating is with respect to the baseline value.
Only those patients with both a baseline and post-treatment measurement are included.

Patient's global assessment of disease activity (VAS mm) by visit (ITT population, LOCF)

	Lumiracoxib 100mg o.d. N=427	Celecoxib 200mg o.d. N=419	Placebo N=416
Baseline			
n	427	419	416
Mean	62.2	63.1	60.2
Visit 3 (Week 4)			
n	427	419	416
Mean	41.4***	43.0***	49.8
Mean change	-20.8	-20.1	-10.4
Visit 4 (Week 8)			
n	427	419	416
Mean	38.1***	40.3***	48.7
Mean change	-24.1	-22.8	-11.5
Visit 5 (Week 13)			
n	427	419	416
Mean	38.9***	38.9***	46.9
Mean change	-23.3	-24.2	-13.3

Symbols: comparison with placebo, ANCOVA, *p<0.05, **p<0.01, ***p<0.001; p-values not adjusted for multiplicity.
Note: Change of pain rating is with respect to the baseline value.
Only those patients with both a baseline and post-treatment measurement are included.

Physician's global assessment of disease activity (VAS mm) by visit (ITT population, LOCF)

	Lumiracoxib 100mg o.d. N=427	Celecoxib 200mg o.d. N=419	Placebo N=416
Baseline			
n	427	419	416
Mean	61.8	61.1	60.4
Visit 3 (Week 4)			
n	425	418	416
Mean	40.9***	41.0***	48.4
Mean change	-20.9	-20.1	-12.0
Visit 4 (Week 8)			
n	425	418	416
Mean	37.8***	38.5***	47.2
Mean change	-24.0	-22.7	-13.2
Visit 5 (Week 13)			
n	425	418	416
Mean	37.5***	36.6***	45.8
Mean change	-24.3	-24.5	-14.6

Symbols: comparison with placebo, ANCOVA, *p<0.05, **p<0.01, ***p<0.001; p-values not adjusted for multiplicity.
Note: Change of pain rating is with respect to the baseline value.
Only those patients with both a baseline and post-treatment measurement are included.

Overall OA pain intensity in the target hip (VAS mm) by visit (ITT population, LOCF)

	Lumiracoxib 100mg o.d. N=427	Celecoxib 200mg o.d. N=419	Placebo N=416
Baseline			
n	427	419	416
Mean	71.0	70.5	70.4
Visit 3 (Week 4)			
n	427	419	416
Mean	42.5***	41.8***	49.9
Mean change	-28.5	-28.6	-20.5
Visit 4 (Week 8)			
n	427	419	416
Mean	39.2***	38.2***	47.1
Mean change	-31.8	-32.3	-23.3
Visit 5 (Week 13)			
n	427	419	416
Mean	38.8***	37.1***	46.1
Mean change	-32.2	-33.4	-24.3

Symbols: comparison with placebo, ANCOVA, *p<0.05, **p<0.01, ***p<0.001; p-values not adjusted for multiplicity.
Note: Change of pain rating is with respect to the baseline value.
Only those patients with both a baseline and post-treatment measurement are included.

Safety Results

Adverse Events by System Organ Class

	Lumiracoxib 100mg o.d. N=427 n (%)	Celecoxib 200mg o.d. N=419 n (%)	Placebo N=416 n (%)
Total no. of patients with AEs	241 (56.4)	222 (53.0)	198 (47.6)
Primary system organ class affected:			
Musculoskeletal and connective tissue disorders	78 (18.3)	80 (19.1)	74 (17.8)
Nervous system disorders	72 (16.9)	67 (16.0)	60 (14.4)
Gastrointestinal disorders	67 (15.7)	60 (14.3)	55 (13.2)
Infections and infestations	63 (14.8)	66 (15.8)	53 (12.7)
General disorders and administration site conditions	37 (8.7)	33 (7.9)	21 (5.0)
Injury, poisoning and procedural complications	20 (4.7)	13 (3.1)	12 (2.9)
Investigations	20 (4.7)	14 (3.3)	12 (2.9)
Respiratory, thoracic and mediastinal disorders	14 (3.3)	16 (3.8)	15 (3.6)
Skin and subcutaneous tissue disorders	13 (3.0)	15 (3.6)	11 (2.6)
Vascular disorders	11 (2.6)	2 (0.5)	7 (1.7)
Metabolism and nutrition disorders	10 (2.3)	6 (1.4)	5 (1.2)
Reproductive system and breast disorders	9 (2.1)	1 (0.2)	1 (0.2)
Renal and urinary disorders	8 (1.9)	3 (0.7)	3 (0.7)
Ear and labyrinth disorders	6 (1.4)	1 (0.2)	3 (0.7)
Eye disorders	6 (1.4)	7 (1.7)	4 (1.0)
Psychiatric disorders	6 (1.4)	9 (2.1)	10 (2.4)
Cardiac disorders	5 (1.2)	3 (0.7)	2 (0.5)
Neoplasms benign, malignant and unspecified (including cysts and polyp)	3 (0.7)	1 (0.2)	5 (1.2)
Endocrine disorders	1 (0.2)	1 (0.2)	1 (0.2)
Immune system disorders	1 (0.2)	3 (0.7)	3 (0.7)
Blood and lymphatic system disorders	0 (0.0)	1 (0.2)	0 (0.0)
Hepatobiliary disorders	0 (0.0)	0 (0.0)	1 (0.2)

Frequency of AEs by primary system organ class is presented in descending order for the Lumiracoxib 100mg o.d. treatment group.

10 Most Frequent AEs for any group by preferred term

	Lumiracoxib 100mg o.d. N=427 n (%)	Celecoxib 200mg o.d. N=419 n (%)	Placebo N=416 n (%)
Headache	59 (13.8)	47 (11.2)	46 (11.1)
Back pain	22 (5.2)	35 (8.4)	29 (7.0)
Pain in extremity	18 (4.2)	19 (4.5)	11 (2.6)
Arthralgia	16 (3.7)	26 (6.2)	22 (5.3)
Diarrhea	16 (3.7)	9 (2.1)	17 (4.1)
Nasopharyngitis	16 (3.7)	10 (2.4)	15 (3.6)
Upper respiratory tract infection	13 (3.0)	5 (1.2)	10 (2.4)
Nausea	11 (2.6)	12 (2.9)	10 (2.4)
Oedema peripheral	11 (2.6)	10 (2.4)	7 (1.7)
Dyspepsia	10 (2.3)	13 (3.1)	11 (2.6)

Frequency of AEs by primary system organ class is presented in descending order for the Lumiracoxib 100mg o.d. treatment group.

Serious Adverse Events and Deaths

	Lumiracoxib 100 mg o.d.	Celecoxib 200 mg o.d.	Placebo
No. (%) of subjects studied	427 (100)	419 (100)	416 (100)
No. (%) of subjects with AE(s)	241 (56.4)	222 (53.0)	198 (47.6)
Number (%) of subjects with serious or other significant events			
Death	0 (0.0)	2 (0.5)	0 (0.0)
Non-fatal SAE(s)	8 (1.9)	2 (0.5)	9 (2.2)
Discontinued due to SAE(s)	2 (0.5)	3 (0.7)	2 (0.5)

Cause of Death
Celecoxib 200 mg: 1 sudden cardiac death, 1 arteriosclerotic cardiovascular disease

SAEs that occurred during the trial:
Lumiracoxib 100 mg: 1 renal colic, 1 hypertension, 1 arthralgia, 1 intervertebral disc protrusion, 1 lumbar spinal stenosis, 1 benign prostatic hyperplasia, 1 osteoarthritis, 1 dysphagia
Celecoxib 200 mg: 1 pneumonia aspiration, 1 cervical vertebral fracture
Placebo: 1 lacunar infarction, 1 pelvic fracture, 1 pharyngolaryngeal pain, 1 rotator cuff syndrome, 1 inguinal hernia, 1 breast cancer, 1 spinal column stenosis, 1 hip arthroplasty, 1 arthralgia

Other Relevant Findings None
Date of Clinical Trial Report 10-Jan-2007
Date Inclusion on Novartis Clinical Trial Results Database 17-Oct-2007
Date of Latest Update 08-Oct-2007