Sponsor

Novartis

Generic Drug Name

Lumiracoxib.

Therapeutic Area of Trial

Post surgical arthroscopic pain.

Approved Indication

Registered indications worldwide (varies by country):

- Symptomatic treatment of osteoarthritis
- Treatment of acute pain
- Treatment of primary dysmenorrhoea
- Treatment of acute gout

Study Number

CCOX189A2427

Title

A multicenter, randomized, double-blind, placebo controlled, parallel group study to compare efficacy of a single dose of lumiracoxib 400 mg given preemptively versus post-operatively, in reducing pain associated with ambulatory arthroscopic knee surgery.

Phase of Development

Phase IV

Study Start/End Dates

08-Aug-2006 to 15-Dec-2006

Study Design/Methodology

This was a randomized, double-blind, placebo-controlled, parallel group study comparing lumiracoxib 400 mg, given pre-emptively versus post-operatively, in patients of at least 18 years of age who underwent ambulatory arthroscopic knee surgery, with a placebo control. Treatment was a single administration either pre- or post-surgery followed by a 24 hours assessment period.

Centres

3 centers in Germany

Publication

Ongoing

Objectives

Primary objective(s)

- to assess the efficacy of pre-emptive dosing with lumiracoxib 400 mg compared to post-operative dosing with lumiracoxib 400 mg in reducing Pain Intensity (PI) in the target knee after movement at the 2 hour time-point, using a 0-100 mm Visual Analog Scale (VAS), in patients who have had ambulatory arthroscopic knee surgery.

Secondary objective(s)

- to assess, in patients who had ambulatory arthroscopic knee surgery, the efficacy of pre-emptive dosing with lumiracoxib 400 mg compared to post-operative dosing with respect to PI on a 0-100 mm VAS at 1, 2, 3, 4 and 24 hour time-points while at rest and after movement, time to first rescue medication intake, the patient's global evaluation of response to study medication, and to assess the safety and tolerability profile of lumiracoxib.

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

One single dose of oral tablet of 400 mg of lumiracoxib either one hour prior to surgical incision, or 15 minutes after surgery depending on the treatment arm.

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

One single dose of oral tablet of placebo either one hour prior to surgical incision, or 15 minutes after surgery depending of the treatment arm.

Criteria for Evaluation

Primary variables

- pain intensity (PI) after movement 2 hours after surgery.

Assessment of post-operative PI was made using a 0-100 mm visual analog scale (VAS).

Secondary variables

- PI on a 0-100 mm VAS at 1, 2, 3, 4 and 24 hour time-points while at rest
- PI on a 0-100 mm VAS at 1, 3, 4 and 24 hour time-points after movement
- time to first rescue medication intake
- the patient's global evaluation of response to study medication using a 4-point Likert scale.
- to assess the safety and tolerability profile of lumiracoxib.

Safety and tolerability

- vital signs,
- adverse events

- serious adverse events.

Pharmacology

Not applicable.

Other

Not applicable.

Statistical Methods

The primary efficacy variable endpoint was analyzed using a Wilcoxon rank sum test stratified by center (Van Elteren's test) with the normal approximation and locally best weights. If ties occurred, the average rank of the tied values was used, for patients belonging to the intent-to-treat (ITT) population. The comparison of lumiracoxib 400 mg pre-emptive to lumiracoxib 400 mg post-operative was the main contrast of interest. The pairwise comparison of lumiracoxib 400 mg pre-emptive to placebo and lumiracoxib 400 mg post-operative to placebo, was performed to confirm the efficacy of lumiracoxib. For sensitivity reasons the primary analysis was repeated for the per-protocol population.
The following secondary efficacy variables were considered; PI on a VAS at 1,2,3,4 and 24 hours postsurgery whilst at rest, PI on a VAS at 1,3,4 and 24 hours post-surgery after movement, time to first rescue medication intake, global evaluation of response.
Adverse events and vital signs were evaluated for the safety population.

Study Population: Inclusion/Exclusion Criteria and Demographics

The following patients were included in the trial:

- Who had signed a written informed consent before any study procedure was performed.
- Male or female outpatients of at least 18 years of age.
- Who had scheduled minor ambulatory arthroscopic knee surgery, with the exclusion of diagnostic arthroscopy.

The following patients were excluded from the trial:

- Who were pregnant or lactating. Female patients of child-bearing potential must have used a highly reliable method of contraception (Pearl index/ failure rate <1 %) throughout the study.
- With known hypersensitivity to any of the study drugs (including analgesics, antipyretics, narcotics, or non-steroidal anti-inflammatory drugs [NSAIDs] or any cox-2 inhibitors) or to drugs with similar chemical structures.
- Who had experienced, any time in the past, an allergic-type reaction after taking acetylsalicylic acid (ASA)/aspirin or NSAIDs, including but not limited to: asthma, acute rhinitis, nasal polyps, angioneurotic edema, urticaria.
- With evidence of cardiovascular disorder: congestive heart failure (NYHA class II – IV), established ischemic heart disease, peripheral arterial disease or cerebrovascular disease; cardiac dysfunction, cardiac failure or left ventricular dysfunction.
- With evidence of hepatic or gastrointestinal disorder: severe hepatic disease (Child-Pugh >9), history of drug or alcohol abuse within the last 2 years; disease of the gall bladder and pan-

creas; active peptic ulceration within the previous 12 months, gastrointestinal bleeding within the last 5 years (except history of minor lower gastro-intestinal tract bleeding, such as from hemorrhoids or anal fissures) or history of gastro-esophageal reflux disease or hiatus hernia; inflammatory bowel disease.

- With evidence of renal disorder: (estimated creatinine clearance <50 ml/min) or patients with impaired renal function, pre-existing edema or severely dehydrated patients.
- Who had been treated with other investigational drugs at the time of enrollment, or within 30 days or 10 half-lives prior to screening, whichever is longer.
- Who were taking anticoagulants (e.g. warfarin, low-molecular weight heparin) and antiplatelet aggregation agents (except low-dose aspirin 75 mg – 100 mg/ day for cardioprotection).
- With any surgical or medical conditions which, at the discretion of the investigator, could have placed the patient at higher risk from his/her participation in the study, or were likely to prevent the patient from complying with the requirements of the study or completing the trial period.
- With a history of noncompliance to medical regimens and patients who were considered potentially unreliable.
- Who were engaged in disease-related litigation.
- Who had already been randomized to this study for one knee.
- With known reduced CYP2C9 activity.

Number of Subjects

	Lumiracoxib 400 mg pre-emptive	**Lumiracoxib 400 mg post-operative**	**Placebo**
Planned N	44	44	22
Randomised n	45	44	21
Intent-to-treat population (ITT) n (%)	45 (100)	44 (100)	21 (100)
Completed n (%)	45 (100)	44 (100)	21 (100)
Withdrawn n (%)	0 (0)	0 (0)	0 (0)
Withdrawn due to adverse events n (%)	0 (0)	0 (0)	0 (0)
Withdrawn due to lack of efficacy n (%)	0 (0)	0 (0)	0 (0)
Withdrawn for other reasons n (%)	0 (0)	0 (0)	0 (0)

Demographic and Background Characteristics

	Lumiracoxib 400 mg pre-emptive	**Lumiracoxib 400 mg post-operative**	**Placebo**
N (ITT)	45	44	21
Females : males	20 : 25	25 : 19	10 : 11
Mean age, years (SD)	50 (18.16)	51.8 (13.79)	55.8 (9.46)
Mean weight, kg (SD)	79.88 (13.917)	82.11 (15.981)	87.94(16.370)
Race White n (%) Black n (%) Asian n (%)	 45 (100) 0 (0) 0 (0)	 44 (100) 0 (0) 0 (0)	 21 (100) 0 (0) 0 (0)

Other n (%)	0 (0)	0 (0)	0 (0)
BMI, Kg (SD)	27.56 (4.696)	28.01 (5.697)	29.43 (4.428)
Mean duration of surgery (minutes)	31.8	30.6	31.7

Primary Objective Result(s)

Summary statistics for pain intensity (after movement) at 2 hours post-surgery - ITT population, LOCF (Last observation carried forward):

	Lumiracoxib 400 mg pre-emptive	Lumiracoxib 400 mg post-operative	Placebo
Mean (SD)	6.82 (13.36)	9.03 (14.59)	16.00 (24.00)
Median	2.75	3.50	9.00
Interquartile range	6.00	8.00	11.50

Analysis of pain intensity (after movement) at 2 hours post-surgery (ITT population, LOCF):

	Contrast	p-value†	Estimated Difference 95% CI*
Primary contrast			
Lumiracoxib 400mg pre – Lumiracoxib 400mg post	0.602	0.0	-2.0, 1.0
Secondary contrast			
Lumiracoxib 400mg pre – Placebo	0.007	-4.0	-9.0, -1.0
Lumiracoxib 400mg post – Placebo	0.052	-3.5	-8.5, 0.0

† Wilcoxon rank sum test stratified by center.

* 95% CI for the Hodges-Lehmann estimate of the difference.

Secondary Objective Result(s)

Pain intensity (after movement) over time (ITT population, LOCF):

Timepoint (hours post-surgery)		1	2	3	4	24
Lumiracoxib 400 mg preemptive	N†	44	44	43	43	45
	Median	2.00 (A)	2.75 (A)	4.00 (A)	3.75 (A)	5.00 (A)
	IQ range	4.75	6	6.25	7.5	11.5
Lumiracoxib 400 mg post-operative	N†	43	43	43	42	44
	Median	4.50 (A)	3.50 (AB)	3.00 (A)	3.00 (A)	3.00 (A)
	IQ range	13	8	12	10	10.25
Placebo	N†	21	19	19	18	21
	Median	12.00 (B)	9.00 (B)	10.00 (B)	27.50 (B)	12.00 (B)
	IQ range	17	11.5	24	38.5	29

† Observed sample size.

Wilcoxon rank sum test stratified by center.

Note: At each timepoint, letter A indicates the most effective treatment(s), B the next most effective treatment(s), and so forth. Treatments sharing the same letter are not significantly different from each other at the 5% significance level.

Pain intensity (at rest) over time (ITT population, LOCF):

Timepoint (hours post-surgery)		1	2	3	4	24
Lumiracoxib 400 mg preemptive	N†	43	44	43	43	45
	Median	3.00 (A)	3.00 (A)	2.00 (A)	2.00 (A)	2.00 (A)
	IQ range	6	5.5	4.5	5	5
Lumiracoxib 400 mg post-operative	N†	43	43	43	42	44
	Median	3.00 (AB)	3.50 (A)	2.50 (A)	2.50 (A)	2.75 (A)
	IQ range	11	4	4.5	5	6
Placebo	N†	21	19	19	18	21
	Median	6.00 (B)	6.50 (B)	9.00 (B)	14.00 (B)	9.00 (B)
	IQ range	14.5	12.5	15	23	13

† Observed sample size.

Wilcoxon rank sum test stratified by center.

Note: At each timepoint, letter A indicates the most effective treatment(s), B the next most effective treatment(s), and so forth. Treatments sharing the same letter are not significantly different from each other at the 5% significance level.

Time to first use of rescue medication (ITT population):

Treatment	N	n (%)*	Median time (h)	95% CI (h)
Lumiracoxib 400 mg preemptive	45	9 (20.0)	N/A (A)	N/A, N/A
Lumiracoxib 400 mg post-operative	44	7 (15.9)	N/A (A)	N/A, N/A
Placebo	21	11 (52.4)	17.75 (B)	5.75, N/A

* Number (percent) of patients who took rescue medication.

Patients who did not take rescue medication were censored at 24 hours or the last available pain assessment if the patient did not return for the 24 hour assessment.

** Based on logrank test. Survival function(s) corresponding to letter A indicates the most effective treatment(s), B the next most effective treatment(s), and so forth. Treatments sharing the same letter are not significantly different from each other at the 5% significance level.

Summary of patient global evaluation (Intent-to-treat population):

	Lumiracoxib 400 mg	Lumiracoxib 400	Placebo N=21

	preemptive N=45 n (%)	mg post-operative N=44 n (%)	n (%)
Global Evaluation			
Poor	1 (2.2)	1 (2.3)	1 (4.8)
Fair	1 (2.2)	1 (2.3)	3 (14.3)
Good	11 (24.4)	11 (25.0)	9 (42.9)
Excellent	32 (71.1)	31 (70.5)	8 (38.1)
Not Done	0 (0.0)	0 (0.0)	0 (0.0)

Analysis of patient global evaluation using Cochran-Mantel-Haenszel test (ITT population):

Treatment Group	Pairwise Comparison	
	Contrast	p-value*
Lumiracoxib 400mg preemptive	Lum 400mg pre - Lum 400mg post	0.945
	Lum 400mg pre - Placebo	0.012
Lumiracoxib 400mg post-operative	Lum 400mg post - Placebo	0.014

* using the Cochran-Mantel-Haenszel test after adjusting (stratifying) for center.

Safety Results

Adverse Events by System Organ Class

	Lumiracoxib 400 mg preemptive N=45 N (%)	Lumiracoxib 400 mg post-operative N=44 N (%)	Placebo N=21 N (%)
Patients studied			
Randomized patients	45	44	21
Patients with drug-related AE	0 (0.0)	0 (0.0)	0 (0.0)
Drug-related AEs by primary system organ class			
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	0 (0.0)	0 (0.0)	0 (0.0)
General disorders	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac disorders	0 (0.0)	0 (0.0)	0 (0.0)
Vascular disorders	0 (0.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)
Ear and labyrinth disorders	0 (0.0)	0 (0.0)	0 (0.0)
Reproductive system and breast disorders	0 (0.0)	0 (0.0)	0 (0.0)
Renal and urinary disorders	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric disorders	0 (0.0)	0 (0.0)	0 (0.0)
Immune system disorders	0 (0.0)	0 (0.0)	0 (0.0)

10 Most Frequently Reported AEs Overall by Preferred Term n (%)

	Lumiracoxib 400 mg preemptive N=45 n (%)	Lumiracoxib 400 mg post-operative N=44 n (%)	Placebo N=21 n (%)
Angina pectoris	0 (0.0)	0 (0.0)	1 (4.8)
Abdominal pain	0 (0.0)	1 (2.3)	0 (0.0)
Vomiting	1 (2.2)	0 (0.0)	0 (0.0)
Headache	1 (2.2)	1 (2.3)	0 (0.0)

Serious Adverse Events and Deaths

	Lumiracoxib 400 mg preemptive N=45 n (%)	Lumiracoxib 400 mg post-operative N=44 n (%)	Placebo N=21 n (%)
No. (%) of subjects studied	45	44	21
No. (%) of subjects with AE(s)	2 (4.4)	2 (4.5)	1 (4.8)
Number (%) of subjects with serious or other significant events	n (%)	n (%)	n (%)
Death	0 (0.0)	0 (0.0)	0 (0.0)
SAE(s)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued due to SAE(s)	0 (0.0)	0 (0.0)	0 (0.0)

Other Relevant Findings

None

Date of Clinical Trial Report

17 July 2007

Date Inclusion on Novartis Clinical Trial Results Database

12 December 2007

Date of Latest Update

12 December 2007