Sponsor Novartis
Generic Drug Name Lumiracoxib
Therapeutic Area of Trial Gout
Approved Indication Registered indications worldwide (varies by country): • Symptomatic treatment of osteoarthritis (OA) • Symptomatic treatment of rheumatoid arthritis (RA) • Treatment of acute pain • Treatment of primary dysmenorrhoea
Study Number CCOX189A2426
Title A 1-week, multi-center, randomized, double-blind, double-dummy, active-controlled, parallel trial of lumiracoxib (400 mg od) in patients with acute flares of gout, using indomethacin (50 mg tid) as a comparator.
Phase of Development Phase 4
Study Start/End dates 27-Jun-2005 / 11-Nov-2005
Study Design/Methodology This was a multi-center, randomized, double-blind, double-dummy, parallel group trial. Patients were assessed within 48 hours of gout onset for pain intensity, joint tenderness, joint swelling and erythema in the affected joint. Patients who met the entry criteria were then randomized 1:1 to treatment with lumiracoxib 400 mg once daily (od) or indomethacin 50 mg three times daily (tid) for 1 week.
Centres 39 centers in Argentina (2) and Germany (37)
Objectives Primary outcome/efficacy objective(s) To compare lumiracoxib 400 mg od with 50 mg tid indomethacin in the treatment of acute gout with respect to the mean change from baseline in pain intensity over Days 2 to 5, assessed in the study joint approximately 4 hours after the first daily dose of study medication on each day. Secondary outcome/efficacy objective(s) Secondary objectives were: 1. To assess the safety and tolerability profile of lumiracoxib in comparison to indomethacin. 2. To explore the efficacy of lumiracoxib 400 mg od as compared to indomethacin 50 mg tid with respect to the mean change from baseline of pain intensity in the study joint over the entire treatment period 2-7 days. 3. To assess the efficacy of lumiracoxib as compared to indomethacin by visit with respect to:

- Patient's global assessment of response to therapy.
- Physician's global assessment of response to therapy.
- Physician's assessment of tenderness of study joint.
- Physician's assessment of swelling of study joint.
- C-reactive protein level.
- Proportion of patients who discontinued treatment because of a lack of efficacy.
- Usage of rescue medication.

4. Health survey questionnaires: SF-36 and EQ-5D.

Test Product, Dose, and Mode of Administration

Lumiracoxib 400 mg tablets taken orally once daily

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

Indomethacin 50 mg capsules taken orally three times daily (tid)
Placebo matching lumiracoxib
Placebo matching indomethacin

Criteria for Evaluation

Primary efficacy:

The primary efficacy variable was the mean change from baseline in pain intensity over days 2-5, assessed on a 5-point Likert scale (calculated as baseline – mean pain intensity on days 2, 3, 4 and 5).

Secondary efficacy:

1. Mean change of pain intensity in the study joint from baseline over days 2-7.
2. Average patient's global assessment of response to therapy over days 2-5 and days 2-7.
3. Average Physician's global assessment of response to therapy over days 2 and 5 and days 2, 5 and end of study.
4. Average Physician's assessment of tenderness of study joint over days 2 and 5 and days 2, 5 and end of study.
5. Average Physician's assessment of swelling of study joint over days 2 and 5 and days 2, 5 and end of study.
6. C-reactive protein level at end of study.
7. Proportion of patients who discontinued treatment because of a lack of efficacy.
8. Usage of rescue medication. All patients will be categorized as having taken or not analgesic rescue medication.
9. Average Physician's assessment of erythema of study joint over days 2 and 5 and days 2, 5 and end of study.
10. Health survey questionnaires: SF-36 and EQ-5D

Safety/tolerability:

The assessment of safety was based mainly on the frequency of adverse events and on the number of laboratory values that fell outside of pre-determined ranges. Data from vital signs were also collected and notable values were flagged.

Statistical Methods

All data from all study centers were combined and summarized by Novartis personnel. Demographic and background characteristics were summarized.

The primary efficacy variable was the mean change of pain intensity from baseline over days 2-5,

assessed on a 5-point Likert scale (calculated as baseline – mean pain intensity on day 2, 3, 4 & 5). A statistical hypothesis test was carried out by means of a confidence interval approach commonly used for the analysis of non-inferiority trials on the per-protocol population.

Secondary variables included patient's and physician's global assessment of response to therapy, and physician's assessment of erythema, tenderness and swelling. These particular secondary variables were analyzed by analysis of covariance with treatment group and center as fixed effects and baseline value and mono/polyarticular gout as covariates.

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 any AE, and having an AE in each body system. Laboratory data were listed; notable (outside pre-determined ranges) and abnormal (outside normal ranges) laboratory values were summarized. Vital signs data were listed and notable values flagged.

No interim analysis was performed.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

1. Ambulatory cooperative male or female patients of at least 18 years of age.
2. Acute attack of gout in 4 joints or less, diagnosed clinically according to the ACR 1977 classification criteria and with an onset within the last 48 hours prior to evaluation. Where more than one joint was involved, the most affected joint was to be identified, as the study joint, at baseline and followed throughout the study.
3. Acute pain intensity of at least moderate in severity at baseline. The baseline pain intensity (PI) assessment was to be taken at least:
    a. 4 hours after the last dose of ≤ 400 mg ibuprofen, ≤ 1 g paracetamol, ≤ 600 mg aspirin or ≤ 2 tablets of other over-the-counter analgesic aspirin-based or paracetamol-based combination medications, or
    b. 8 hours after the last dose of > 400 mg ibuprofen, ≤ 50 mg diclofenac, or
    c. 12 hours after the last dose of > 500 mg naproxen.
4. Females were eligible only, if they were neither pregnant (β-hCG serum pregnancy test negative) nor lactating, and were either:
    a. surgically sterilized (tubal ligation or hysterectomy),
    b. postmenopausal for at least 24 months past last natural menses,
    c. postmenopausal with last natural menses in the past 24 months, and
        i. with an FSH > 40 IU/L and serum estradiol < 18 pg/ml, or
        ii. with an FSH ≤ 40 IU/L and serum estradiol ≥ 18 pg/ml, and using an acceptable form of birth control,
    d. premenopausal and using an acceptable form of birth control.
5. Signed informed consent before entering the study.

Exclusion criteria

1. Acute attack of gout before the last 48 hours prior to evaluation.
2. Polyarticular gout involving > 4 joints.
3. Rheumatoid arthritis, infectious arthritis, pseudo-gout or other acute inflammatory arthritides.
4. Use of non-steroidal anti-inflammatory drugs in the previous 24 hours (other than ibuprofen, paracetamol, aspirin, diclofenac, naproxen as described above).
5. Use of etoricoxib in the previous 48 hours.

6. Systemic use or intra-articular injection (in the previous 4 weeks) of steroids.
7. Clinically significant hepatic disease or renal disease.
8. Impaired renal function taking ACE-inhibitors.
9. Inflammatory bowel disease.
10. Previous or active peptic ulceration or clinically significant GI bleeding.
11. Asthma, acute rhinitis, nasal polyps, angioneurotic edema, urticaria or other allergic-type reactions after taking aspirin, paracetamol/ acetaminophen, any NSAIDs and/or COX-2 inhibitors.
12. Known hypersensitivity to lumiracoxib, indomethacin and/or paracetamol/ acetaminophen.
13. Treatment with an investigational drug within the prior month or 10 half-lives, whichever was longer.
14. Use of: Lithium, warfarin, any coumarin related therapy, or similar anticoagulants, or phenytoin
15. Involvement in health-related litigation.
16. History of:
    - attacks of gout known to be unresponsive to NSAIDs,
    - malignancy of any organ system, treated or untreated, within the previous five years whether or not evidence of local recurrence or metastases exists were excluded (with the exception of localized basal cell carcinoma of the skin),
    - coronary heart disease with electrocardiogram (ECG) derived evidence of silent myocardial ischemia,
    - congestive heart failure with symptoms at rest or with minimal activity (NYHA class III-IV),
    - unstable angina,
    - variant angina (Prinzmetal's angina)
    - drug or alcohol abuse.
17. Allopurinol or colchicine treatment was allowed if the dose had been stable for ≥ 2 weeks prior to baseline for allopurinol or ≥ 4 weeks prior to baseline for colchicine and remained unchanged throughout the 7 days of the study.
18. Significant medical problems, including but not limited to the following: uncontrolled hypertension, heart failure, type I diabetes (well controlled type II diabetes was allowed even when insulin was required), thyroid disease (unless the patient was on controlled thyroid hormone for at least 3 months), active hepatic disease, known HIV seropositivity, epilepsy, parkinsonism, psychiatric disturbance.
19. History of cardiac and cerebral thrombotic/ischemic diseases and/or events were excluded from the study:
    - Angina pectoris (of any severity) or other evidence of coronary heart disease,
    - Myocardial infarction,
    - Coronary artery bypass grafting (CABG) or percutaneous coronary intervention (any PCI procedure),
    - Transient ischemic attack,
    - Clinically significant carotid artery stenosis or history of carotid endarterectomy,
    - Ischemic stroke,
    - Congestive heart failure, NYHA class III – IV.

Number of Subjects	Lum 400mg od	Ind 50mg tid
Planned N	117	117

Randomised n	118	117
Completed n (%)	116 (98.3)	107 (91.5%)
Withdrawn n (%)	2 (1.7)	10 (8.5)
Included in the primary analysis n (%)	118 (100)	117 (100)
Withdrawn due to adverse events n (%)	2 (1.7)	7 (6.0)
Withdrawn due to lack of efficacy n (%)	0	1 (0.9)
Withdrawn for other reasons n (%)	0	2 (1.8)
Demographic and Background Characteristics		
N (ITT)	118	117
Females: males	81:37	80:37
Mean age, years (SD)	56.8 (14.06)	56.1 (13.29)
Mean weight, kg (SD)	87.3 (15.12)	84.1 (13.66)
Race White n (%) Black n (%) Asian n (%) Other n (%)	 116 (98.3) 0 (0.0) 1 (0.8) 1 (0.8)	 116 (99.1) 0 (0.0) 1 (0.9) 0 (0.0)

Primary Efficacy Result(s)–per protocol population

Change from baseline in pain intensity over days 2-5: treatment comparison	Estimated difference	95% Confidence interval	p-value	Outcome
Contrast: Lumiracoxib 400 mg od vs. indomethacin 50 mg tid	-0.004	-0.207, 0.199	0.967	non-inferiority shown (Non-inferiority of Lum 400mg od to Ind 50mg tid can be claimed if the lower limit of the CI is > -0.5

Secondary efficacy result(s)–per protocol population

	Estimated difference	95% Confidence interval	p-value
• Change from baseline in pain intensity over days 2-7: Contrast: Lumiracoxib 400 mg od vs. indomethacin 50 mg tid	-0.027	-0.218, 0.164	0.782
• Patient's global assessment of response to therapy over days 2-5: Contrast: Lumiracoxib 400 mg od vs. indomethacin 50 mg tid	-0.023	-0.219, 0.173	0.814
• Patient's global assessment of response to therapy over days 2-7: Contrast: Lumiracoxib 400 mg od vs. indomethacin 50 mg tid	-0.033	-0.221, 0.156	0.733
• Physician's global assessment of response to therapy over days 2 and 5: Contrast: Lumiracoxib 400 mg od vs. indomethacin 50 mg tid	-0.001	-0.203, 0.202	0.994

• Physician's global assessment of response to therapy over days 2, 5 and end of study: Contrast: Lumiracoxib 400 mg od vs. indomethacin 50 mg tid	-0.016	-0.202, 0.170	0.866
• Physician's assessment of tenderness of study joint over days 2 and 5: Contrast: Lumiracoxib 400 mg od vs. indomethacin 50 mg tid	0.072	-0.065, 0.209	0.303
• Physician's assessment of tenderness of study joint over days 2, 5 and end of study: Contrast: Lumiracoxib 400 mg od vs. indomethacin 50 mg tid	0.035	-0.088, 0.159	0.575
• Physician's assessment of swelling of study joint over days 2 and 5: Contrast: Lumiracoxib 400 mg od vs. indomethacin 50 mg tid	0.056	-0.082, 0.194	0.421
• Physician's assessment of swelling of study joint over days 2, 5 and end of study: Contrast: Lumiracoxib 400 mg od vs. indomethacin 50 mg tid	0.056	-0.060, 0.171	0.343
• Physician's assessment of erythema of study joint over days 2 and 5: Contrast: Lumiracoxib 400 mg od vs. indomethacin 50 mg tid	-0.025	0.072, -0.122	0.608
• Physician's assessment of erythema of study joint over days 2, 5 and end of study: Contrast: Lumiracoxib 400 mg od vs. indomethacin 50 mg tid	-0.024	-0.096, 0.049	0.515
• Patient's health status using the SF-36 (physical component) score at end of study: Contrast: Lumiracoxib 400 mg od vs. indomethacin 50 mg tid	-0.493	-2.524, 1.538	0.633
• Patient's health status using the SF-36 (mental component) score at end of study: Contrast: Lumiracoxib 400 mg od vs. indomethacin 50 mg tid	0.171	-1.808, 2.150	0.865
• Patient's health status using the EQ-5D score at end of study: Contrast: Lumiracoxib 400 mg od vs. indomethacin 50 mg tid	-0.016	-0.058, 0.027	0.470
• Analysis of C-reactive protein level at end of study: Contrast: Lumiracoxib 400 mg od vs. indomethacin 50 mg tid	2.610	-0.275, 5.495	0.076
• Analysis of proportion of patients who took rescue medication: Contrast: Lumiracoxib 400 mg od vs. indomethacin 50 mg tid	1.67 (estimated odds ratio)	0.77, 3.63	0.196

• Discontinuation due to lack of efficacy		An analysis of the proportion of patients who discontinued treatment because of a lack of efficacy was planned, but insufficient data was available to perform this analysis.	

Adverse Events by System Organ Class

Total number of patients studied	Lum 400mg od N=118 n (%)	Ind 50mg tid N=117 n (%)
Patients with AEs	12 (10.2)	26 (22.2)
GI disorders	8 (6.8)	11 (9.4)
Nervous system disorders	1 (0.8)	8 (6.8)
Psychiatric disorders	1 (0.8)	3 (2.6)
Ear and labyrinth disorders	0 (0.0)	8 (6.8)
General disorders and administration site conditions	0 (0.0)	5 (4.3)
Investigations	0 (0.0)	3 (2.6)

Frequency of AEs by primary system organ class is presented in descending order for the lumiracoxib group

Safety Results

10 Most Frequently Reported AEs Overall by Preferred Term	Lum 400mg od	Ind 50mg tid
Total number of patients with AEs	12 (10.2)	26 (22.2)
Vertigo	0 (0.0)	8 (6.8)
Abdominal pain upper	1 (0.8)	5 (4.3)
Headache	1 (0.8)	5 (4.3)
Dizziness	0 (0.0)	2 (1.7)
Flatulence	0 (0.0)	2 (1.7)
Fatigue	0 (0.0)	2 (1.7)
Additional AEs occurred only in single patients and are therefore not listed here.		

Serious Adverse Events and Deaths

There were no deaths and no SAEs for any patients during the study. There was one SAE reported for a patient in the indomethacin group after he had discontinued from the study. This patient is not included in the summary tables or listings.

Date Inclusion on Novartis Clinical Trial Results Database
30-Nov-2006