Sponsor
Novartis

Generic Drug Name
Lumiracoxib

Therapeutic Area of Trial
Primary osteoarthritis of hip, knee, hand or spine

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
CCOX189A2369

Title

A 52-week, international, multicenter, randomized, double-blind, double-dummy, parallel-group clinical trial to compare retention on treatment, safety, tolerability and efficacy of lumiracoxib 100mg od, lumiracoxib 100mg bid and celecoxib 200mg od in patients with primary osteoarthritis of hip, knee, hand or spine

Phase of Development

Phase III

Study Start/End Dates

First patient enrolled: 07-Sep-2004

Last patient completed: 21-Nov-2005

Study Design/Methodology

This was a 52 week, international, multicenter, randomized, double-blind, double-dummy, parallel-group study of two doses of lumiracoxib, 100mg od and 100mg bid, using celecoxib 200mg od as active comparator in patients with primary osteoarthritis (OA) in the hip, knee, hand or spine. One joint was identified as the target joint and was evaluated throughout the study. Patients underwent a 3-7 day analgesic/NSAID wash-out period before randomization when only paracetamol/acetaminophen was allowed as analgesic rescue medication. Gastrointestinal (GI), cardiovascular/cerebrovascular (CCV) and Liver pre-defined events were adjudicated by external blinded safety committees. Patients were followed up for CCV events until the completion of the intended 52 week study period regardless of the time of study drug discontinuation.

Centres

214 centers in 7 countries: Belgium (11 centers), Canada (45 centers), Germany (7 centers), France (13 centers), Italy (25 centers), Switzerland (9 centers), USA (104)

Objectives

Primary outcome/efficacy objective(s)

- To compare lumiracoxib 100mg once daily (od), lumiracoxib 100mg twice daily (bid) and celecoxib 200mg od with respect to the retention rate at 1 year using non-inferiority analysis (defined as the proportion of patients staying in the study up to the end of study visit) in patients suffering from primary osteoarthritis in hip, knee, hand or spine.

Secondary outcome/efficacy objective(s)

- To collect and compare safety and tolerability data in a large group of patients using lumiracoxib versus patients using celecoxib.
- To compare efficacy of treatment with lumiracoxib versus treatment with celecoxib with respect to Patient's assessment of osteoarthritis pain, Patient's global assessment of disease activity, and Physician's global assessment of disease activity.
- To evaluate the use of paracetamol/acetaminophen rescue medication.
- To validate the psychometric properties of the Short Arthritis assessment Scale (SAS) by analyzing patient reported outcomes collected in this study.

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

lumiracoxib 100mg od tablet, taken once a day in the morning;

lumiracoxib 100mg bid tablets taken 1 in the morning and 1 in the evening.

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

Celecoxib 200mg od tablet, taken once a day in the morning.

Criteria for Evaluation

Retention on treatment:

The primary evaluation was the retention rate at 1 year. Reasons for discontinuation were evaluated as a secondary objective.

Secondary efficacy:

Efficacy was assessed as a secondary objective using the patient's OA pain assessment in the target joint, the physician's and patient's global assessments of disease activity, the need for analgesic rescue medication and the scores from the Short Arthritis assessment Scale. OA pain and disease activity assessments used 5-point Likert scales. Scores used were 1,2,3,4 and 5 for the five Likert scale categories none/very good to extreme/very poor, respectively; the lower the score the better the response.

Safety/tolerability:

Safety was assessed by evaluation of adverse events, results of physical examinations, data on vital signs, and data from laboratory evaluations.

Pharmacology:

No pharmacology evaluations were performed in this study.

Other:

N/A

Statistical Methods

All data from all study centers were combined and summarized by Novartis personnel. The primary variable was retention on treatment at 1 year in the ITT population. If a patient discontinued the study prior to the end of study visit (allowed time window 50 to 53 weeks) the variable retention on treatment was set to "no", otherwise to "yes". Discontinuation from the study was taken as the time when the patient stopped taking study medication.

Non-inferiority of lumiracoxib 100mg od and 100mg bid versus celecoxib 200mg od was tested by comparing pairwise differences in retention rates at 1 year using a multiple testing procedure to adjust for multiplicity and a confidence interval (CI) approach with Delta (Δ) set at -10% (-0.10 when expressed as a fraction of 1). If the lower limit of the two-sided 97.5% CI for the difference in retention rates was above Δ then non-inferiority was shown, if the lower limit of the two-sided 97.5% CI was above 0 then superiority could be claimed. Sensitivity analyses were performed in the PP and PP2 populations. The data were described using cumulative Kaplan-Meier estimates at weeks 4, 13, 20, 26, 39 and 52 for the ITT and PP populations.

All statistical tests for secondary endpoints and secondary efficacy variables were performed at the 5% significance level without adjusting for multiplicity.

A competing risks model was applied to estimate the risk of discontinuing for a specific reason taking into account the risk of discontinuing for other reasons in the ITT population. The Aalen-Johansen estimator was presented with 95% CIs for discontinuations due to: 1) AEs, 2) abnormal laboratory values, 3) unsatisfactory therapeutic effect, 4) elevated CV risk or history of CCV disease, 5) withdrawal of consent as a result of the news about COX-2 inhibitors.

For the ITT population, retention on treatment was also analyzed using a multiple logistic regression model with treatment as main effect and age as covariate. Odds ratios and 95% CIs were presented for all between-treatment pair-wise comparisons.

The secondary efficacy variables, patient's OA target joint pain intensity, patient's and physician's global assessments of disease activity, were summarized as the weighted average over the treatment period (sum of values at each timepoint multiplied by the time since previous visit divided by the total time in the study), representing an integrated measure of the overall level of efficacy experienced during the treatment period. These overall effects were analyzed by an analysis of covariance (ANCOVA) with treatment as main effect and the respective baseline value, age and center as covariates. Treatment comparison was performed using least squares means (LSMs) obtained from the model, 95% CIs for the difference in LSMs were presented.

In addition, OA pain intensity, and patient's and physician's global assessments of disease activity were classified as "improved", "worsened" or "unchanged" if the endpoint assessment improved by 1 category on the Likert scale, worsened by 1 category or remained unchanged, respectively. Treatment comparisons of improvement rates were made using a multiple logistic regression model with treatment as main effect and age as covariate. Odds ratios and 95% CIs were presented for the ITT, PP2 and DISC populations. Missing baseline assessments were replaced by the median of the baseline assessments. For missing post-baseline values occurring before discontinuation from the study, the last observation carried forward (LOCF) technique was used.

The dichotomous outcome variable, use of rescue medication, was analyzed using a multiple logistic regression model with baseline pain intensity and treatment as main effects. Odds ratios and 95% CIs were presented for all between-treatment pair-wise comparisons in the ITT, PP2 and DISC populations.

Short Arthritis assessment Scale scores were analyzed in the ITT population by using an analysis of covariance fitting the baseline value, country and treatment as factors. A patient's questionnaire was considered as "valid" if not more than 1 question was missing. Single items missing were replaced by the median of all observations at that timepoint/visit across all patients.

Safety data were summarized descriptively presenting frequencies by treatment in the safety population. GI, CCV and Liver events meeting pre-defined criteria were assessed by independent safety committees and separate summaries of these events and their adjudications were provided.

No interim analyses were performed.

Study Population: Inclusion/Exclusion Criteria and Demographics

Patients included were male or female outpatients aged ≥40 years with active primary OA in any one of the following joints; hip, knee, hand, cervical or lumbar spine and symptoms for at least 3 months, who required NSAID therapy, had baseline pain assessment (Likert scale) in the affected joint of mild, moderate or severe and had given written informed consent. Only one joint was defined as the target joint which was evaluated throughout the study. Following Protocol Amendment 2, patients who were moderately above average risk or high risk of cardiovascular (CV) disease (as defined in the Multiple Risk Factor Assessment Equations) or had a history of CCV disease were no longer eligible for participation in this study and such ongoing patients were discontinued.

Number of Subjects

Patient disposition (Randomized population)

	Lumiracoxib 100mg od n (%)	Lumiracoxib 100mg bid n (%)	Celecoxib 200mg od n (%)	Total n (%)
Number (%) of patients:				
Randomized	**757 (100)**	**1520 (100)**	**759 (100)**	**3036 (100)**
Completed	**355 (46.9)**	**728 (47.9)**	**344 (45.3)**	**1427 (47.0)**
Total discontinued	**402 (53.1)**	**792 (52.1)**	**415 (54.7)**	**1609 (53.0)**
Primary reason for discontinuation:				
Death	**0**	**2 (0.1)**	**0**	**2 (0.1)**
Adverse event(s)	**96 (12.7)**	**187 (12.3)**	**89 (11.7)**	**372 (12.3)**
Abnormal laboratory value(s)	**8 (1.1)**	**16 (1.1)**	**4 (0.5)**	**28 (0.9)**
Abnormal test procedure result(s)	**0**	**0**	**1 (0.1)**	**1 (0.0)**
Unsatisfactory therapeutic effect	**97 (12.8)**	**158 (10.4)**	**88 (11.6)**	**343 (11.3)**
Condition no longer requires treatment	**0**	**3 (0.2)**	**2 (0.3)**	**5 (0.2)**
Protocol violation(s)	**12 (1.6)**	**23 (1.5)**	**11 (1.4)**	**46 (1.5)**
Patient withdrew consent	**78 (10.3)**	**170 (11.2)**	**93 (12.3)**	**341 (11.2)**
Lost to follow-up	**9 (1.2)**	**7 (0.5)**	**8 (1.1)**	**24 (0.8)**
Administrative problems	**102 (13.5)**	**226 (14.9)**	**119 (15.7)**	**447 (14.7)**
Discontinuation related to news about COX-2 inhibitors †	**115 (15.2)**	**267 (17.6)**	**130 (17.1)**	**512 (16.9)**
Administrative problems: due to elevated CV risk or history of CCV disease	**90 (11.9)**	**199 (13.1)**	**103 (13.6)**	**392 (12.9)**
Patient withdrew consent	**25 (3.3)**	**68 (4.5)**	**27 (3.6)**	**120 (4.0)**

† According to Protocol Amendment 2 resulting from news surrounding COX-2 inhibitors.
Note: Data regarding the number of patients who died are collected from the study completion page. This table does not include deaths occurring after study discontinuation.

Demographic and Background Characteristics (Safety population)

	Lumiracoxib 100mg od N=755	Lumiracoxib 100mg bid N=1519	Celecoxib 200mg od N=758	Total N=3032
Age (years)				
n	**755**	**1519**	**758**	**3032**
mean (SD)	**62.9 (10.25)**	**62.2 (10.02)**	**62.7 (10.00)**	**62.5 (10.07)**
Sex – n (%)				
Male	**214 (28.3)**	**438 (28.8)**	**227 (29.9)**	**879 (29.0)**
Female	**541 (71.7)**	**1081 (71.2)**	**531 (70.1)**	**2153 (71.0)**
Race – n (%)				
White/Caucasian	**712 (94.3)**	**1450 (95.5)**	**731 (96.4)**	**2893 (95.4)**
Black/African American	**22 (2.9)**	**45 (3.0)**	**13 (1.7)**	**80 (2.6)**
Japanese	**1 (0.1)**	**1 (0.1)**	**0 (0.0)**	**2 (0.1)**
Other Asian/Pacific Islander	**6 (0.8)**	**7 (0.5)**	**1 (0.1)**	**14 (0.5)**
Hispanic	**10 (1.3)**	**8 (0.5)**	**11 (1.5)**	**29 (1.0)**
Other	**4 (0.5)**	**8 (0.5)**	**2 (0.3)**	**14 (0.5)**
Height (cm)				

n	**751**	**1513**	**754**	**3018**
mean (SD)	**165.1 (9.26)**	**165.6 (9.62)**	**165.2 (9.12)**	**165.4 (9.41)**
Weight (kg)				
n	**753**	**1512**	**755**	**3020**
mean (SD)	**80.7 (19.78)**	**81.7 (19.72)**	**81.2 (18.21)**	**81.3 (19.37)**
BMI (kg/m^2)				
n	**750**	**1510**	**754**	**3014**
mean (SD)	**29.5 (6.41)**	**29.7 (6.34)**	**29.8 (6.33)**	**29.7 (6.35)**
Low-dose aspirin use – n (%)	**151 (20.0)**	**324 (21.3)**	**171 (22.6)**	**646 (21.3)**
Current smoker – n (%)	**86 (11.4)**	**169 (11.1)**	**85 (11.2)**	**340 (11.2)**
Alcohol intake – n (%)				
<1 drink/day	**660 (87.4)**	**1326 (87.3)**	**663 (87.5)**	**2649 (87.4)**
1-2 drinks/day	**79 (10.5)**	**170 (11.2)**	**82 (10.8)**	**331 (10.9)**
≥3 drinks/day	**16 (2.1)**	**23 (1.5)**	**13 (1.7)**	**52 (1.7)**

Primary Efficacy Result(s)

Retention on treatment at 1 year: treatment comparisons (ITT, PP and PP2 populations)

Population Treatment group	N	Retention rate n (%)	Contrasts	Estimated difference	97.5% CI of difference	Outcome†
ITT						
LUM 100mg od	**755**	**354 (46.9)**	**LUM 100mg od - CEL 200mg od**	**0.02**	**-0.04 , 0.07**	**Non-inferiority shown**
LUM 100mg bid	**1519**	**722 (47.5)**	**LUM 100mg bid - CEL 200mg od**	**0.02**	**-0.03 , 0.07**	**Non-inferiority shown**
CEL 200mg od	**758**	**343 (45.3)**				
PP						
LUM 100mg od	**648**	**315 (48.6)**	**LUM 100mg od - CEL 200mg od**	**0.02**	**-0.04 , 0.08**	**Non-inferiority shown**
LUM 100mg bid	**1310**	**639 (48.8)**	**LUM 100mg bid - CEL 200mg od**	**0.02**	**-0.03 , 0.07**	**Non-inferiority shown**
CEL 200mg od	**675**	**315 (46.7)**				
PP2						
LUM 100mg od	**550**	**315 (57.3)**	**LUM 100mg od - CEL 200mg od**	**0.00**	**-0.06 , 0.07**	**Non-inferiority shown**
LUM 100mg bid	**1072**	**639 (59.6)**	**LUM 100mg bid - CEL 200mg od**	**0.03**	**-0.03 , 0.08**	**Non-inferiority shown**
CEL 200mg od	**552**	**315 (57.1)**				

Secondary efficacy result(s)

Summary of patient's target joint OA pain assessment, patient's and physician's global assessments of disease activity at study endpoint (ITT population)

	Lumiracoxib 100mg od N=755 n (%)	Lumiracoxib 100mg bid N=1519 n (%)	Celecoxib 200mg od N=758 n (%)
Patient's target joint OA pain assessment			
Improved	**382 (50.6)**	**795 (52.3)**	**406 (53.6)**
Unchanged	**269 (35.6)**	**566 (37.3)**	**265 (35.0)**
Worsened	**104 (13.8)**	**158 (10.4)**	**87 (11.5)**
Patient's global assessment of disease activity			
Improved	**368 (48.7)**	**768 (50.6)**	**373 (49.2)**
Unchanged	**265 (35.1)**	**534 (35.2)**	**269 (35.5)**
Worsened	**122 (16.2)**	**216 (14.2)**	**116 (15.3)**
Physician's global assessment of disease activity			
Improved	**411 (54.5)**	**888 (58.5)**	**425 (56.2)**
Unchanged	**244 (32.4)**	**463 (30.5)**	**232 (30.7)**
Worsened	**99 (13.1)**	**167 (11.0)**	**99 (13.1)**

Note: "Improved" corresponds to assessments at study endpoint in a lower severity of pain category or a better disease activity category than at baseline (i.e. lower scores at study endpoint than baseline) and vice versa for "worsened". Patients with missing baseline assessments are not included.

Integrated measure of patient's target joint OA pain, patient's and physician's global assessments of disease activity: treatment comparisons using analysis of covariance (ITT population)

Variable Treatment group	N	Weighted average ‡ LSM score	Contrasts	Difference of LSMs	95% CI of difference	P-value †
Patient's target joint OA pain assessment						
LUM 100mg od	**755**	**2.78**	**LUM 100mg od - CEL 200mg od**	**0.00**	**-0.07 - 0.07**	**0.9169**
			LUM 100mg od - LUM 100mg bid	**0.05**	**-0.01 - 0.12**	**0.0819**
LUM 100mg bid	**1519**	**2.72**	**LUM 100mg bid - CEL 200mg od**	**-0.05**	**-0.11 - 0.01**	**0.1051**
CEL 200mg od	**758**	**2.77**				
Patient's global assessment of disease activity						
LUM 100mg od	**755**	**2.61**	**LUM 100mg od - CEL 200mg od**	**0.00**	**-0.07 - 0.08**	**0.9072**
			LUM 100mg od - LUM 100mg bid	**0.06**	**-0.00 - 0.13**	**0.0509**
LUM 100mg bid	**1519**	**2.54**	**LUM 100mg bid - CEL 200mg od**	**-0.06**	**-0.12 - 0.00**	**0.0688**
CEL 200mg od	**758**	**2.60**				
Physician's global assessment of disease activity						
LUM 100mg od	**755**	**2.55**	**LUM 100mg od - CEL 200mg od**	**0.03**	**-0.04 - 0.10**	**0.4471**
			LUM 100mg od - LUM 100mg bid	**0.10**	**0.03 - 0.16**	**0.0026***
LUM 100mg bid	**1519**	**2.45**	**LUM 100mg bid - CEL 200mg od**	**-0.07**	**-0.13 - -0.01**	**0.0328***
CEL 200mg od	**758**	**2.52**				

LUM = lumiracoxib, CEL = celecoxib
Note: Scores used were 1,2,3,4, and 5 for the five Likert scale categories none/very good to extreme/very poor, respectively; the lower the score the better the response. The categorical data collected were converted to continuous data for the summaries and analyses.
‡ The integrated measure was defined as weighted average of post-baseline scores up to end of study using the LOCF principle and with time since previous visit as weight; missing baseline values were substituted by the median of the baseline values in the ITT population.
† The ANCOVA model considers treatment as main effect and the respective baseline value, age, center as covariates. * p<0.05 (no adjustment for multiplicity)

Use of analgesic rescue medication - Treatment comparisons using logistic regression (ITT population)

Contrast	N	n (%)	Odds ratio	95% CI for odds ratio	p-value
Lumiracoxib 100mg od	755	600 (79.5)			
Celecoxib 200mg od	758	616 (81.3)			
LUM 100mg od vs CEL 200mg od			0.91	0.70 - 1.18	0.4653
Lumiracoxib 100mg bid	1519	1224 (80.6)			
Celecoxib 200mg od	758	616 (81.3)			
LUM 100mg bid vs CEL 200mg od			0.93	0.74 - 1.17	0.5267
Lumiracoxib 100mg od	755	600 (79.5)			
Lumiracoxib 100mg bid	1519	1224 (80.6)			
LUM 100mg od vs LUM 100mg bid			0.98	0.78 - 1.23	0.8682

Short Arthritis assessment Scale total score - Treatment comparisons using analysis of covariance Visit: Week 52 (ITT population)

	First group of contrast		Second group of contrast		Difference of LS	95% CI for difference in	
Contrast	N	LSM	N	LSM	means	LS means	p-value
LUM 100mg od - CEL 200mg od	755	13.12	758	12.54	0.58	-0.70 - 1.87	0.3747
LUM 100mg bid - CEL 200mg od	1519	12.87	758	12.54	0.34	-0.78 - 1.46	0.5549
LUM 100mg od - LUM 100mg bid	755	13.12	1519	12.87	0.25	-0.86 - 1.36	0.6645

Safety Results

Adverse Events by System Organ Class (Safety population)

	Lumiracoxib 100mg od n (%)	Lumiracoxib 100mg bid n (%)	Celecoxib 200mg od n (%)
Total patients studied	**755 (100)**	**1519 (100)**	**758 (100)**
Patients with AE(s)	**548 (72.6)**	**1078 (71.0)**	**526 (69.4)**
Primary system organ class affected:			
Infections and infestations	**252 (33.4)**	**487 (32.1)**	**245 (32.3)**
Gastrointestinal disorders	**212 (28.1)**	**403 (26.5)**	**188 (24.8)**
Musculoskeletal and connective tissue disorders	**176 (23.3)**	**334 (22.0)**	**165 (21.8)**
Nervous system disorders	**132 (17.5)**	**300 (19.7)**	**136 (17.9)**

General disorders and administration site conditions	**77 (10.2)**	**174 (11.5)**	**75 (9.9)**
Injury, poisoning and procedural complications	**71 (9.4)**	**162 (10.7)**	**65 (8.6)**
Respiratory, thoracic and mediastinal disorders	**75 (9.9)**	**153 (10.1)**	**78 (10.3)**
Investigations	**55 (7.3)**	**135 (8.9)**	**47 (6.2)**
Skin and subcutaneous tissue disorders	**43 (5.7)**	**91 (6.0)**	**51 (6.7)**
Vascular disorders	**32 (4.2)**	**78 (5.1)**	**43 (5.7)**
Psychiatric disorders	**39 (5.2)**	**65 (4.3)**	**31 (4.1)**
Ear and labyrinth disorders	**20 (2.6)**	**57 (3.8)**	**22 (2.9)**
Cardiac disorders	**18 (2.4)**	**46 (3.0)**	**21 (2.8)**
Metabolism and nutrition disorders	**23 (3.0)**	**44 (2.9)**	**21 (2.8)**
Eye disorders	**15 (2.0)**	**43 (2.8)**	**14 (1.8)**
Renal and urinary disorders	**24 (3.2)**	**43 (2.8)**	**25 (3.3)**
Neoplasms benign, malignant and unspecified (incl cysts and polyp	**10 (1.3)**	**26 (1.7)**	**15 (2.0)**

Primary system organ classes (SOCs) are listed in order of decreasing frequency for lumiracoxib 100mg bid. All deaths occurring before database lock are included.

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

	Lumiracoxib 100mg od n (%)	Lumiracoxib 100mg bid n (%)	Celecoxib 200mg od n (%)
Total patients studied	**755 (100)**	**1519 (100)**	**758 (100)**
Patients with AE(s)	**548 (72.6)**	**1078 (71.0)**	**526 (69.4)**
AE preferred terms:			
Gastrointestinal disorders:			
Abdominal pain upper	**42 (5.6)**	**88 (5.8)**	**35 (4.6)**
Dyspepsia	**38 (5.0)**	**85 (5.6)**	**39 (5.1)**
Nausea	**25 (3.3)**	**58 (3.8)**	**24 (3.2)**
Diarrhea	**32 (4.2)**	**55 (3.6)**	**23 (3.0)**
General disorders and administration site conditions:			
Infections and infestations:			
Nasopharyngitis	**80 (10.6)**	**141 (9.3)**	**75 (9.9)**
Upper respiratory tract infection	**36 (4.8)**	**86 (5.7)**	**43 (5.7)**
Urinary tract infection	**38 (5.0)**	**75 (4.9)**	**24 (3.2)**
Musculoskeletal and connective tissue disorders:			
Back pain	**46 (6.1)**	**87 (5.7)**	**52 (6.9)**
Arthralgia	**53 (7.0)**	**82 (5.4)**	**41 (5.4)**
Nervous system disorders:			
Headache	**82 (10.9)**	**174 (11.5)**	**82 (10.8)**

Preferred terms are listed in order of decreasing frequency for lumiracoxib 100mg bid within each primary system organ class. All deaths occurring before database lock are included.

Deaths, non-fatal SAEs and other clinically significant AEs (safety population)

	Lumiracoxib 100mg od n (%)	Lumiracoxib 100mg bid n (%)	Celecoxib 200mg od n (%)
Total patients studied	**755 (100)**	**1519 (100)**	**758 (100)**
Patients with serious AEs:			
Deaths †	**2 (0.3)**	**7 (0.5)**	**1 (0.1)**
deaths reported on study completion page	**0**	**2 (0.1)**	**0**
deaths after discontinuation	**2 (0.3)**	**5 (0.3)**	**1 (0.1)**
SAE(s) (fatal and/or non-fatal)	**41 (5.4)**	**72 (4.7)**	**48 (6.3)**
Patients with other significant AEs:			
Discontinuations due to any AEs	**98 (13.0)**	**193 (12.7)**	**87 (11.5)**
discontinuations due to SAE(s)	**20 (2.6)**	**28 (1.8)**	**14 (1.8)**
discontinuations due to non-serious AE(s)	**81 (10.7)**	**166 (10.9)**	**73 (9.6)**
Discontinuations due to abnormal lab values	**7 (0.9)**	**16 (1.1)**	**4 (0.5)**
AEs causing temporary interruption of study drug	**68 (9.0)**	**137 (9.0)**	**86 (11.3)**
Prespecified AE(s) ‡	**194 (25.7)**	**377 (24.8)**	**169 (22.3)**
Adjudicated GI events	**15 (2.0)**	**17 (1.1)**	**10 (1.3)**
definite, probable or possible UGIT or LGIT ulcer complications	**8 (1.1)**	**10 (0.7)**	**2 (0.3)**
symptomatic ulcer of UGIT	**1 (0.1)**	**2 (0.1)**	**3 (0.4)**
Adjudicated CCV events up to week 52	**7 (0.9)**	**13 (0.9)**	**7 (0.9)****
adjudicated CCV events during the study	**5 (0.7)**	**7 (0.5)**	**3 (0.4)**
confirmed, probable or possible APTC $ events during the study	**4 (0.5)**	**6 (0.4)**	**2 (0.3)**
adjudicated CCV events between discontinuation and week 52 follow-up call	**3 (0.4)**	**6 (0.4)**	**5 (0.7)****
confirmed, probable or possible APTC $ events between discont. and week 52	**3 (0.4)**	**4 (0.3)**	**3 (0.4)****
Adjudicated Liver events: AST/ALT>3xULN and probably or possibly related to study drug	**11 (1.5)**	**35 (2.3)**	**3 (0.4)**

Counts of significant AEs are not mutually exclusive; patients may have >1 type of significant event.
† All deaths occurring before database lock are included. Deaths reported as the primary reason for discontinuation are collected from the study completion page. Deaths occurring after permanent discontinuation from the study are collected from the AE page.
‡ Gastrointestinal (GI), cardiovascular/cerebrovascular (CCV) and Liver pre-defined events
U/LGIT: upper/lower gastrointestinal tract
$ Antiplatelet Trialists' Collaboration: Patients with confirmed, probable or possible CCV death, stroke or MI.
**** Includes patient with confirmed MI on day 0, but did not take study drug**

Other Relevant Findings

Date of Clinical Trial Report

10 July 2006

Date Inclusion on Novartis Clinical Trial Results Database

30-Nov-2006

Date of Latest Update

30-Nov-2006