Sponsor

Novartis

Generic Drug Name

Lumiracoxib

Trial Indication(s)

Not applicable

Protocol Number

CCOX189A2483

Protocol Title

A retrospective pharmacogenetics analysis of patients with elevated liver enzymes (Hy's law cases or AST/ALT > 5x ULN) in clinical studies CCOX189A0117, CCOX189A2332, CCOX189A2369, CCOX189A0126, CCOX189A0112, CCOX189A0109, CCOX189A2361, CCOX189A0104, CCOX189A0112E1, CCOX189A0128, CCOX189A2316, CCOX189A2364, CCOX189A2360E1 or CCOX189A2361E1

Clinical Trial Phase

Phase IV

Study Start/End Dates

01 Dec 2009 to 10 Aug 2011

Reason for Termination (If applicable)

Not Applicable

Study Design/Methodology

Multicenter, Retrospective, Post-hoc pharmacogenetic sub-study was a follow-up study including up to 97 male and female patients with elevated liver enzymes (Hy's law cases or AST/ALT > 5xULN) in previous lumiracoxib studies.

Centers

45 centers in 20 countries: Belgium (1), Brazil (1), Canada (4), China (1), Colombia (1), Czech Republic (1), Denmark (2),Finland (1), France (4), Germany (3), Italy (1), Netherlands (3), Peru (1), Russia (2), Spain (2), Sweden (1), Switzerland (1), Taiwan (1), UK (2), and US (12)

Objectives:

Primary Objective:

To determine whether patients who experienced hepatotoxicity when taking lumiracoxib were carriers of the DQA1*0102 allele.

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

Not applicable, no study drug was provided.

Statistical Methods

In the primary analysis the number and frequency of DQA1*0102 carriers (i.e. patients who carry at least one copy of the DQA1*0102 allele) among genotyped Hy's law patients were tabulated. The number and frequency of each specific DQA1 genotype were also tabulated within this population. The same tabulations were performed for the ALT/AST >10xULN, >8xULN, and > 5xULN populations. These results were also tabulated for individual races. All statistics were descriptive. The secondary variable was the patient's genotype for the UGT1A1 gene. The number of copies of the UGT1A1*28 allele was recorded for each Hy's Law patient. All statistics were descriptive.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria:

- Patients were included who had received lumiracoxib and experienced a Hy's law or AST/ALT > 5xULN event after initiating treatment in clinical studies CCOX189A0117, CCOX189A2332, CCOX189A2369, CCOX189A0126, CCOX189A0112, CCOX189A0109, CCOX189A2361, CCOX189A0104, CCOX189A0112E1, CCOX189A0128, CCOX189A2316, CCOX189A2364, CCOX189A2360E1 or CCOX189A2361E1.
- Only patients who agreed to participate in this pharmacogenetic post-hoc study by signing the informed consent form were included in this study.

Exclusion criteria:

- Patients who did not provide written informed consent.

Participant Flow Table

Number of patients enrolled in CCOX189A2483 study by ALT/AST elevation category

ALT/AST elevation category	Number of patients (%)
Total patients enrolled	53
Hy's Law	4 (7.5%)
> 10 times ULN (but not Hy's Law)	15 (28.3%)
> 8 times but ≤10 times ULN	7 (13.2%)
> 5 times but ≤8 times ULN	27 (50.9%)

Baseline Characteristics

Demographics of the CCOX189A2483 study population

	Number of patients
Total	53
Gender	
Female	39 (73.6%)
Male	14 (26.4%)
Age, mean (SD)	63.1 (9.0)
Race	
Caucasian	47 (88.7%)
Asian	3 (5.7%)
Hispanic	2 (3.8%)
Black	1 (1.9%)

Summary of Efficacy

Primary Outcome Result:

Sensitivity of HLA-DQA1*0102 allele in CCOX189A2483 and the original TARGET pharmacogenetic sub-study

	CCOX189A2483 study		Original TARGET PG sub-study	
Patient population[1]	Sensitivity (allele carriers / total patients)	95% confidence interval[2]	Sensitivity (allele carriers / total patients)	95% confidence interval[2]
Hy's Law[3]	75.0% (3/4)		100% (3/3)	
ALT/AST >10 times ULN	84.2% (16/19)	60.4%, 96.6%	23/25 (92.0%)	74.0%, 99.0%
ALT/AST >8 times ULN	80.8% (21/26)	60.7%, 93.4%	31/34 (91.2%)	76.3%, 98.1%
ALT/AST >5 times ULN	81.1% (43/53)	68.0%, 90.6%	53/63 (84.1%)	72.8%, 92.1%

[1]Patient populations are cumulative: patient population with >5 times ULN includes the patient populations with >8 and >10 times ULN and Hy's Law; patient population with >8 times ULN includes the patient population with >10 times ULN and Hy's Law; patient population with >10 times ULN includes Hy's Law
[2]Confidence interval calculated by exact binomial method
[3]ALT and/or AST >3 times ULN and serum bilirubin ≥2 times ULN. Confidence intervals were not calculated for patients meeting Hy's Law criteria because of small sample size

Sensitivity of the HLA-DQA1*0102 allele by race

Patient population[1]	Sensitivity of HLA-DQA1*0102 allele (no. of carriers / total no. of patients)			
	Caucasian	Asian	Hispanic	Black
Hy's Law[2]	100% (2/2)	100% (1/1)	0% (0/1)	N/A
ALT/AST >10 times ULN	88.2% (15/17)	100% (1/1)	0% (0/1)	N/A
ALT/AST >8 times ULN	83.3% (20/24)	100% (1/1)	0% (0/1)	N/A
ALT/AST >5 times ULN	85.1% (40/47)	66.7% (2/3)	0% (0/2)	100% (1/1)

[1]Patient populations are cumulative: patient population with >5 times ULN includes the patient populations with >8 and >10 times ULN and Hy's Law; patient population with >8 times ULN includes the patient population with >10 times ULN and Hy's Law; patient population with >10 times ULN includes Hy's Law
[2]ALT and/or AST >3 times ULN and serum bilirubin ≥2 times ULN.

Summary of Safety

Safety Results

Adverse Events were not collected

Serious Adverse Events and Deaths

No serious adverse event was reported.

No death was reported.

Other Relevant Findings

Not applicable

Date of Clinical Trial Report.

02 Aug 2012