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MERCK RESEARCH LABORATORIES

ABBREVIATED CLINICAL STUDY REPORT

MK-0782
L-001069957 Tablet
Osteoarthritis or Rheumatoid Arthritis

PROTOCOL TITLE/NO.: A Multicenter, Randomized, Parallel-Group, Active-Controlled Double-Blind Study Conducted Under In-House Blinding Conditions to Determine the Incidence of Gastroduodenal Ulcers in Patients With Osteoarthritis or Rheumatoid Arthritis After 12 Weeks of Treatment With L-001069957 21 mg Plus Low-Dose Aspirin, L-001069957 42 mg Plus Low-Dose Aspirin, Celecoxib 400 mg Plus Low-Dose Aspirin, or Low-Dose Aspirin Alone #003

INVESTIGATOR(S)/STUDY CENTER(S): Eight investigators (domestic only) [3.5; 3.6; 4.4]

PUBLICATION(S): None

PROTECTION OF HUMAN SUBJECTS: This study was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research. For study audit information see [3.1][1]. All subjects signed an informed consent prior to initiation of any study procedures [3.3.1; 3.3.2]. This study included the collection of genomic samples. Patients were consented separately for genomic sample collection [3.3.3; 3.3.4; 3.3.5], and participation in the primary study was not contingent upon participation in the genomic component.

PRIMARY THERAPY PERIOD: 19-Aug-2004 to 4-Oct-2004. Last patient out 5-Nov-2004. Frozen file occurred 12-Nov-2004.	**CLINICAL PHASE:** IIa

DURATION OF TREATMENT: Following a 14-day washout period, primary therapy was scheduled to last 12 weeks. However, due to early termination of the L-001069957 program, no patient actually received prime therapy for longer than 43 days.

HYPOTHESES AND OBJECTIVE(S):

Primary Objective: To determine the comparative cumulative incidence of gastric and/or duodenal ulcers (≥3 mm) following administration over 12 weeks of L-001069957 21 mg plus enteric-coated (EC) aspirin 100 mg once daily, L-001069957 42 mg plus EC aspirin 100 mg once daily, celecoxib 200 mg twice daily plus EC aspirin 100 mg once daily, and EC aspirin 100 mg once daily.

Secondary Objective: To assess the general safety and tolerability of L-001069957 21 mg plus EC aspirin 100 mg once daily and L-001069957 42 mg plus EC aspirin 100 mg once daily.

Primary Hypothesis: Compared to celecoxib 200 mg twice daily plus EC aspirin 100 mg once daily, the cumulative percentage of patients with osteoarthritis (OA) or rheumatoid arthritis (RA) who develop gastric and/or duodenal ulcers (≥3 mm) after 12 weeks of treatment will be lower with L-001069957 42 mg plus EC aspirin 100 mg once daily.

[1] Refer to List of Appendices. Within a bracket, the first number refers to an Appendix Category, the second number refers to an Appendix within that Category, and the third number (optional) refers to a document within the Appendix, e.g., [1.1.3] = Appendix Category 1, Appendix 1, Document No. 3.

Secondary Hypotheses: (a) Compared to celecoxib 200 mg twice daily plus EC aspirin 100 mg once daily, the cumulative percentage of patients with OA or RA who develop gastric and/or duodenal ulcers (≥3 mm) after 12 weeks of treatment will be lower with L-001069957 21 mg plus EC aspirin 100 mg once daily; (b) L-001069957 21 mg plus EC aspirin 100 mg once daily and L-001069957 42 mg plus EC aspirin 100 mg once daily will be generally safe and well tolerated.

STUDY STATUS: The study was discontinued when the company notified Regulatory agencies of its decision to voluntarily withdraw VIOXX (rofecoxib) worldwide and terminate all clinical studies with VIOXX and NO-Rofecoxib (L-001069957) on 30-Sep-2004. Insufficient data was obtained to conduct statistical analyses.

STUDY DESIGN: This was a multicenter, randomized, parallel-group, active-controlled, double-blind study conducted under in-house blinding conditions to evaluate the gastrointestinal safety of L-001069957 plus low-dose aspirin compared to celecoxib plus low-dose aspirin and low-dose aspirin alone in patients who had been clinically diagnosed with either osteoarthritis (OA) or rheumatoid arthritis (RA) for at least 6 months prior to Visit 1.0. It was requested that sites attempt to insure that a minimum of 30% of patients enrolled had a primary diagnosis of rheumatoid arthritis; this was the targeted final distribution of patients study-wide. Enrolled patients required either chronic NSAID or selective COX-2 inhibitor therapy and may or may not have had a medical requirement for chronic aspirin therapy. It was required for sites to ensure that not more than 20% of patients enrolled be on chronic aspirin therapy at Visit 1.0. The enrollment period was to be ~8 months and the duration of treatment 12 weeks. At randomization, patients were stratified according to their history of significant upper gastrointestinal (GI) mucosal disease (upper GI perforation, clinical gastroduodenal ulcer, upper GI hemorrhage, or pyloric obstruction [PUB]) [3.8; 3.9].

Following a 14 day wash-out period, patients with confirmed OA or RA underwent an upper endoscopy [3.2; 3.4] If negative for gastroduodenal ulcers and erosive esophagitis, they received L-001069957 21 mg plus EC aspirin 100 mg once daily, L-001069957 42 mg plus EC aspirin 100 mg once daily, celecoxib 200 mg twice daily plus EC aspirin 100 mg once daily, or EC aspirin 100 mg alone once daily. Additional upper endoscopies were to be performed at Weeks 6 and 12, and at discontinuation visits should patients discontinue early. Patients were evaluated every 3 weeks while on treatment and all patients were to be followed from enrollment to completion or early discontinuation. Routine clinical and laboratory examinations were performed to assess safety and tolerability. This study included the collection of genomic samples [3.2].

At the time the company terminated the study, all patients enrolled in the trial were instructed to discontinue study therapy. Discontinuation visit procedures were performed and all unused study drug returned.

ULCERS AND EROSIONS: The primary endpoint in this study was the development of a gastric and/or duodenal ulcer during the treatment period. Erosions and ulcers were defined as white based circumscribed mucosal breaks, erosions being flat and ulcers demonstrating unequivocal evidence of depth and measuring ≥3 mm in the greatest dimension (length) by close application of an open endoscopic biopsy forcep provided by Merck [3.2]. At the Visit 2.0 baseline endoscopy, patients were not randomized if a gastric, esophageal and/or duodenal ulcer, endoscopically evident pyloric obstruction, or erosive esophagitis were present.

SUBJECT/PATIENT DISPOSITION:

	Total	EC ASA 100 mg Once Daily	L-001069957 21 mg + EC ASA 100 mg Once Daily	L-001069957 42 mg + EC ASA 100 mg q.d.	Celecoxib 200 mg Twice Daily + EC ASA 100 mg Once Daily
RANDOMIZED:	49	13	10	11	15
Male (age range)	19 (51-79)	3 (66-79)	5 (54-66)	4 (52-67)	7 (51-71)
Female (age range)	30 (45-75)	10 (46-75)	5 (45-69)	7 (56-74)	8 (52-72)
Mean Age	61.0	63.8	59.1	61.5	59.3
COMPLETED:	0	0	0	0	0
DISCONTINUED:	49	13	10	11	15
Clinical adverse experience	0	0	0	0	0
Laboratory adverse experience	0	0	0	0	0
Other*	49	13	10	11	15

* All 49 patients were discontinued early; 48 due to early termination of the clinical trial and one patient was lost to follow-up.

Data Source: [4.1; 4.3; 4.2; 4.4; 4.5]

DOSAGE/FORMULATION NOS.: The patient received study drug packaged in a blinded 7-day supply child-resistant blister card containing 7 rows and 5 columns (Column A L-001069957 21 mg or placebo, Column B L-001069957 42 mg or placebo, Column C celecoxib 200 mg or placebo, Column D aspirin 100 mg, Column E celecoxib 200 mg or placebo). One row equaled one day of medication. The patient was instructed to take medication from Columns A, B, C, and D every morning and medication from Column E at bedtime [3.9].

Acetaminophen/paracetamol 325-mg tablets were provided as open-label escape medication in bottles of tablets. The patient was instructed to take 2 tablets per dose as directed for arthritis pain only and not to take more than 8 tablets per day.

The antacid Maalox™ Plus (Rhone-Poulenc Rorer, 50 tablets per box) or Gelusil™ (Warner Lambert Consumer Healthcare, 100 tablets per box) were given as open-label escape medication for p.r.n. use for minor upper GI dyspeptic symptoms possibly due to NSAID, aspirin, or COX-2 inhibitor use. The antacid was not to be used with any other antacid nor in the period 3 hours before through 3 hours after the morning dose of medication from blister cards. The formulation numbers for the study treatments are provided in Appendix [3.7].

DIAGNOSIS/INCLUSION CRITERIA: Patients were males or females who were ≥45 years of age (or would reach 45 years of age during the ~16-week course of study), who had been clinically diagnosed with either osteoarthritis (OA) or rheumatoid arthritis (RA) for at least 6 months prior to Visit 1.0. Enrolled patients required either chronic NSAID or selective COX-2 inhibitor therapy and may or may not have had a medical requirement for chronic aspirin therapy. Patients were required to have normal esophageal, gastric and duodenal mucosa at the Visit 2.0 baseline endoscopy and meet the specific inclusion/exclusion criteria described in the protocol [3.2].

EVALUATION CRITERIA: Efficacy: Efficacy in the treatment of OA or RA was not an objective of this study. A patient global assessment of disease status/activity was to be obtained at screening (Week -2), baseline (Week 0) and at Weeks 3, 6, 9, and 12 to assure adequate pain control and continued ability to participate in the study. Safety: In all patients, endoscopy was to be performed at baseline (Week 0), Week 6, and Week 12, or at the time of discontinuation should a patient discontinue early. Patients would self-monitor for clinical adverse experiences during the entire study period. Safety endpoints were the proportion of patients with: 1 or more clinical adverse experiences; drug-related (possibly, probably, or definitely) clinical adverse experiences; serious clinical adverse experiences; discontinued due to a clinical adverse experience, discontinued due to an adverse experience in the gastrointestinal system; edema-related adverse experiences; discontinued due to edema-related adverse experiences; hypertension-related adverse experiences; discontinued due to hypertension-related adverse experiences; adverse experiences of congestive heart failure; exceeding the predefined limits of change for hemoglobin, hematocrit, ALT, AST, and creatinine. All patients were to be assessed by physical examination, vital signs, weight, serum chemistry, complete blood count (CBC) with differential and platelet counts, urinalysis, serum and urine β-hCG (females of childbearing potential only), stool Hemoccult™, and ECG. At Week 3, a 3 hour postdose (~Cmax) ECG would be obtained to evaluate the patient's QTc interval plus a pharmacokinetic (PK) blood sample for possible rofecoxib assay.

STATISTICAL PLANNING AND ANALYSIS: The study planned to enroll ~1136 evaluable patients, divided in a 1:1:1:1 ratio between 4 treatment groups (284 projected evaluable patients each) at ~100 domestic and international sites. At the time the clinical study was terminated, 49 domestic and 0 international patients had been enrolled. Of these, only 3 patients had reached the Study Week 6 endoscopy. No efficacy or statistical analyses were performed due to insufficient data on endpoints. Safety information was evaluated by tabulating adverse experiences.

RESULTS: All allocated patients were discontinued due to program termination by the company on 30-Sep-2004. The duration of treatment on study drug for randomized patients ranged from 2 to 43 days. Safety and tolerability were assessed for all patients by clinical review of all safety parameters including adverse experiences, laboratory values, and vital signs. A gastric and/or duodenal ulcer was the predefined endpoint of the study and was not to be separately reported as an adverse experience unless it met the regulatory definition for a serious adverse experience [3.2]. Only 3 patients had a post-randomization endoscopy. Normal esophageal, gastric and duodenal mucosa were reported. No analyses were performed due to insufficient data on endpoints.

Five patients reported one or more clinical adverse experiences (Table 1); none resulted in discontinuation. [redacted] Listings of reported clinical adverse experiences may be found in Appendix [4.6].

Table 1

Clinical Adverse Experience Summary

	EC ASA 100 mg Once Daily (N = 13)		L-001069957 21 mg + EC ASA 100 mg Once Daily (N = 10)		L-001069957 42 mg + EC ASA 100 mg Once Daily (N = 11)		Celecoxib 200 mg Twice Daily + EC ASA 100 mg Once Daily (N = 15)	
	n	(%)	n	(%)	n	(%)	n	(%)
Number (%) of patients:								
With one or more adverse experiences	0	(0.0)	1	(10.0)	1	(9.1)	3	(20.0)
With no adverse experience	13	(100.0)	9	(90.0)	10	(90.9)	12	(80.0)
With drug-related adverse experiences[†]	0	(0.0)	1	(10.0)	0	(0.0)	2	(13.3)

[†] Determined by the investigator to be possibly, probably or definitely drug related.
Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories.

Data Source: [4.5]

There were no serious adverse experiences, deaths, laboratory adverse experiences, or clinical adverse experiences of prolonged QTc interval (the acceptable QTc interval was defined as below 450 msec.). [redacted]

A post hoc analysis of the QTc interval was performed of mean and median values at baseline, Visit 3.0 (treatment)or Visit 6 (post treatment) and change from baseline. There were no apparent differences among treatment groups.

In addition, post hoc analysis of changes in QTc intervals ≥ 30 msec showed only one patient in the L-001065597 21 mg plus EC Aspirin 100 mg treatment group who had a change in QTc interval ≥ 30 msec from baseline at Visit 3.0 (on treatment). However, there were no patients with a change in QTc interval ≥60 msec at Visit 3.0 (on treatment), nor any patients with a change in QTc interval ≥ 30 msec or ≥ 60 msec at Visit 6 (post treatment).

CONCLUSIONS: No conclusions can be drawn based on insufficient data for statistical analyses.

AUTHORS:

[redacted]