

Merck & Co., Inc. Study Synopsis

1. Proprietary Drug Name: Arcoxia	2. <u>Generic Drug Name:</u> ETORICOXIB	3. <u>Therapeutic area and FDA-approved indications:</u> Osteoarthritis (Arcoxia has not been approved by the FDA as of the date of this report)
4. <u>Name of Sponsor/Company:</u> Merck & Co., Inc.		
5. <u>Title of Study:</u> A Multicenter, Randomized, Parallel-Group, 4-Week, Double-Blind and Active Comparator-Controlled Study to Assess the Efficacy, Safety and Tolerability of MK-0663 Tablet 60 mg Once Daily Versus Diclofenac Sodium 75 mg Two Times Daily In the Treatment of Chinese Patients with Osteoarthritis of the Knee or Hip (PN 080; NCT00140972)		
6. <u>Study Investigators/Study Center(s):</u> Multicenter; 6 centers in China		
7. <u>Studied Period (years):</u> <i>(Date of first enrollment) (date of last completed)</i> December 2004 to June 2005		8. <u>Phase of development:</u> Local registration (Phase III) study
9. <u>Primary Hypotheses and Secondary Hypothesis:</u> <p>Primary: 1) To compare the clinical response assessment profile of MK-0663 60 mg once daily to Diclofenac sodium tablet 75 mg two times daily in the treatment of osteoarthritis of the knee or hip during a 4-week treatment period by WOMAC pain subscale. 2) To evaluate the safety and tolerability profile of MK-0663 60 mg administrations for a 4-week period.</p> <p>Secondary: To compare the clinical response assessment profile of MK-0663 60 mg once daily to Diclofenac sodium tablet 75 mg two times daily in the treatment of osteoarthritis of the knee or hip during a 4-week treatment period by the following variables: WOMAC Physical function subscale, WOMAC stiffness subscale. Patient Global Assessment of Response to Therapy, Investigator Global Assessment of Disease Status</p>		

Merck & Co., Inc. Study Synopsis

10. <u>Study Design/ Methodology:</u>	<p>This was a multicenter, randomized, parallel-group, 4-week, double-blind and active comparator-controlled study to evaluate the efficacy, safety and tolerability of MK-0663 60 mg once daily in the treatment of Chinese patients with osteoarthritis of the knee or hip. The primary efficacy endpoints were: WOMAC pain subscale. The secondary efficacy endpoints were: WOMAC Physical function subscale, WOMAC stiffness subscale, Patient Global Assessment of Response to Therapy, Investigator Global Assessment of Disease Status, discontinuation due to lack of efficacy and rescue paracetamol tablet count.</p>																																																								
11. <u>Number of Patients (planned and analyzed):</u>																																																									
	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 30%;"></th> <th style="width: 20%; text-align: center;">Etoricoxib 60mg</th> <th style="width: 20%; text-align: center;">Diclofenac sodium 150mg</th> <th style="width: 30%; text-align: center;">Total</th> </tr> </thead> <tbody> <tr> <td>Randomized</td> <td style="text-align: center;">90</td> <td style="text-align: center;">90</td> <td style="text-align: center;">180</td> </tr> <tr> <td>Male</td> <td style="text-align: center;">17</td> <td style="text-align: center;">12</td> <td style="text-align: center;">29</td> </tr> <tr> <td>Female</td> <td style="text-align: center;">73</td> <td style="text-align: center;">78</td> <td style="text-align: center;">151</td> </tr> <tr> <td>Completed</td> <td style="text-align: center;">84</td> <td style="text-align: center;">87</td> <td style="text-align: center;">171</td> </tr> <tr> <td>Discontinued</td> <td style="text-align: center;">6</td> <td style="text-align: center;">3</td> <td style="text-align: center;">9</td> </tr> <tr> <td>Clinical AE</td> <td style="text-align: center;">4</td> <td style="text-align: center;">0</td> <td style="text-align: center;">4</td> </tr> <tr> <td>Lab AE</td> <td style="text-align: center;">0</td> <td style="text-align: center;">0</td> <td style="text-align: center;">0</td> </tr> <tr> <td>Lack of efficacy</td> <td style="text-align: center;">0</td> <td style="text-align: center;">0</td> <td style="text-align: center;">0</td> </tr> <tr> <td>Lost of follow up</td> <td style="text-align: center;">1</td> <td style="text-align: center;">0</td> <td style="text-align: center;">1</td> </tr> <tr> <td>Withdrew consent</td> <td style="text-align: center;">1</td> <td style="text-align: center;">3</td> <td style="text-align: center;">4</td> </tr> <tr> <td>Protocol deviation</td> <td style="text-align: center;">0</td> <td style="text-align: center;">0</td> <td style="text-align: center;">0</td> </tr> <tr> <td>Safety Set analysis</td> <td style="text-align: center;">90</td> <td style="text-align: center;">90</td> <td style="text-align: center;">180</td> </tr> <tr> <td>Full Analysis Set (FAS)</td> <td style="text-align: center;">90</td> <td style="text-align: center;">90</td> <td style="text-align: center;">180</td> </tr> </tbody> </table>		Etoricoxib 60mg	Diclofenac sodium 150mg	Total	Randomized	90	90	180	Male	17	12	29	Female	73	78	151	Completed	84	87	171	Discontinued	6	3	9	Clinical AE	4	0	4	Lab AE	0	0	0	Lack of efficacy	0	0	0	Lost of follow up	1	0	1	Withdrew consent	1	3	4	Protocol deviation	0	0	0	Safety Set analysis	90	90	180	Full Analysis Set (FAS)	90	90	180
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12. <u>Diagnosis and main criteria for inclusion:</u>	<p>1. Patient was male or female, was at least 40 years of age, and had clinical diagnosis of osteoarthritis of the knee (tibio-femoral joint) or hip for greater than 6 months based on clinical and radiographic criteria. A newly</p>																																																								

Merck & Co., Inc. Study Synopsis

diagnosed patient must have clinical symptoms consistent with osteoarthritis of the study joint for the past 6 months and must also fulfill the criteria specified.

2. The diagnosis of OA was confirmed as ACR functional Class I, II, or III.

3. Patients had demonstrated a clinical response to NSAIDs in the past. In addition, following discontinuation (“washout”) of NSAIDs, patients demonstrated worsening in symptoms as specified by criteria for flare.

13. Test product and reference therapy (if applicable); dose and mode of administration; batch number:

Drug	Potency	Formulation	Dosage form
Etoricoxib	60 mg	MR4903	tablet
Diclofenac sodium	75 mg	MR5095	tablet
Etoricoxib placebo	---	MR4918	Tablet to match etoricoxib 60 mg
Diclofenac sodium placebo	---	MR5070	Tablet to match Diclofenac sodium 75 mg
Paracetamol	325 mg	MR4972	tablet

Batch number: CA-B450 (Etoricoxib and Diclofenac sodium)/CA-B451 (Paracetamol)

14. Duration of treatment: 4 weeks

15. Criteria for Evaluation: **EFFICACY MEASUREMENTS:** The primary efficacy endpoints were: WOMAC pain subscale. The secondary efficacy endpoints were: WOMAC Physical function subscale, WOMAC stiffness subscale, Patient Global Assessment of Response to Therapy, Investigator Global Assessment of Disease Status, discontinuation due to lack of efficacy and rescue paracetamol tablet count.

Merck & Co., Inc. Study Synopsis

SAFETY MEASUREMENTS: Physical examination, vital signs, body weight, electrocardiogram, laboratory safety data (serum chemistry, hematology, urinalysis, urine β -HCG, stool hemocult) and spontaneous reporting of any adverse experiences.

16. Statistical methods:

The analysis populations for the primary and secondary endpoints were the Full Analysis Set (FAS) and Per Protocol Set. The primary efficacy response was the average change from baseline over the 4-week treatment period. (The results of FAS and PP analysis for primary endpoint and FAS analysis for secondary endpoints were demonstrated in Field 17) The treatment response (including WOMAC pain subscale, WOMAC Physical function subscale, WOMAC stiffness subscale, Investigator Global Assessment of Disease Status) within each group was analyzed using Wilcoxon Rank Sum test. The difference of treatment response of all mentioned efficacy variables between the two groups was analyzed using Mann-Whitney test. The proportions of patients with adverse experiences were compared between groups using the Fisher's exact test

Numbers of patients in each of the evaluated populations

	Etoricoxib	Diclofenac	Total
Randomized to treatment group	90	90	180
Safety Set analysis	90	90	180
Full Analysis Set (FAS) analysis	90	90	180
Per Protocol Set (PP) analysis	84	87	171

Merck & Co., Inc. Study Synopsis

17. Summary:

PRIMARY EFFICACY ENDPOINTS

Table 1. The effect analysis of WOMAC Pain Subscale between Etoricoxib and Diclofenac groups (FAS)

WOMAC Pain	The difference of two groups		<i>F</i>	<i>P</i>
	Lease-Squars mean	Confidence Interval		
Baseline-2 weeks	-3.961	-9.872 ~ 1.949	0.081	>0.05
Baseline-4 weeks	-1.559	-7.263 ~ 4.145	0.043	>0.05

* Analysis of Covariance.

Table 2. The effect analysis of WOMAC Pain Subscale between Etoricoxib and Diclofenac groups (PP)

WOMAC Pain	The difference of two groups		<i>F</i>	<i>P</i>
	Lease-Squars mean	Confidence Interval		
Baseline-2 weeks	-4.482	-10.292 ~ 1.528	0.210	>0.05
Baseline-4 weeks	-1.564	-4.030 ~ 7.159	0.068	>0.05

* Analysis of Covariance.

Merck & Co., Inc. Study Synopsis

Secondary Efficacy Endpoints

Table 3. The effect analysis of WOMAC stiffness subscale between Etoricoxib and Diclofenac groups (FAS)

	Etoricoxib			Diclofenac			<i>Z</i> [*]	<i>P</i>
	n	MEAN	SD	n	MEAN	SD		
Baseline-2 weeks	86	19.34	19.49	88	16.73	18.97	0.623	>0.05
Baseline-4 weeks	88	23.52	17.45	90	23.76	21.19	0.193	>0.05

*: Mann-Whitney Test

Table 4 The effect analysis of WOMAC Physical function subscale between Etoricoxib and Diclofenac groups (FAS)

PFTN	Etoricoxib			Diclofenac			<i>Z</i> [*]	<i>P</i>
	n	MEAN	SD	n	MEAN	SD		
Baseline-2 weeks	86	21.50	17.69	88	20.46	16.15	0.114	>0.05
Baseline-4 weeks	88	27.46	15.86	90	26.53	17.13	0.116	>0.05

*: Mann-Whitney Test

Merck & Co., Inc. Study Synopsis

Table 5 The effect analysis of WOMAC scores between Etoricoxib and Diclofenac groups (FAS)

WOMAC	Etoricoxib			Diclofenac			Z^*	P
	n	MEAN	SD	n	MEAN	SD		
Baseline-2 weeks	86	21.57	17.35	88	20.95	15.08	0.039	>0.05
Baseline-4 weeks	88	27.59	15.57	90	27.10	16.24	0.032	>0.05

*: Mann-Whitney Test

Safety

Table 6 Adverse experience incidence between Etoricoxib and Diclofenac groups (SS)

	AE occurred		Non-AE		χ^2	P
	N	%	N	%		
Etoricoxib	21	23.33	69	76.67	0.000	>0.05
Diclofenac	21	23.33	69	76.67		

Merck & Co., Inc. Study Synopsis

Table 7 Drug related adverse experience incidence between Etoricoxib and Diclofenac groups (SS)						
	AE occurred		Non-AE		χ^2	<i>P</i>
	N	%	N	%		
Etoricoxib	16	17.78	74	82.22	2.276	>0.05
18. <u>Date of the report:</u>		20-Jul-07				
19. <u>Contact:</u>		Merck National Service Center 1.800.672.6372				