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Sponsor / Company : Sanofi **Drug Substance : Ketoprofen + Omeprazole**		**Study Identifier : NCT00971581** **Study Code : KETOM_L_04584**
Title of the study:	Safety, tolerability and efficacy of a FDC ketoprofen + omeprazole in patients with rheumatological conditions with a previous history or who are at risk to developing NSAID associated benign gastric ulcers, duodenal ulcers and gastroduodenal erosions in whom continued treatment with NSAID is necessary: open-label, not controlled, phase III study.	
Study center(s):	Number of active centers: 4	
Study period: Date first patient enrolled: 31-Jul-2009. Date last patient completed: 27-May-2010.		
Phase of development: Phase 3		
Objectives:	**Primary objectives** • To confirm the safety and tolerability of a Fixed Dose Combination (FDC) of a Non-Steroidal Anti-Inflammatory Drug (NSAID) (ketoprofen) associated to a Proton Pump Inhibitor (PPI) (omeprazole) in Mexican patients. **Secondary objectives** To confirm the effectiveness of the combination: • Relief of pain [Visual Analogue Scale (VAS)] • Patient's global assessment of disease activity, scored as a scale of 1 (no limitation of normal activities) to 5 (inability to carry out all normal activities)	
Methodology:	National, multicenter, prospective, open label, non-controlled, phase III study conducted in Mexico Duration: 28 days.	
Number of patients:	Planned: 50	Included: 54

Diagnosis and criteria for inclusion:	**Inclusion Criteria:** • Male or female >18 years old. • Adult patient with chronic inflammatory condition, particularly rheumatoid polyarthritis, Ankylosing Spondylitis (or related syndromes like Reiter syndrome or psoriasic arthritis…), with previous history or with risk to develop benign gastric ulcer, duodenal ulcer and gastro duodenal erosions to whom continuous NSAID treatment is needed. • Patients should present at time of inclusion visit, an acute episode, or by recent onset (<48 h) defined as mean pain in last 24 hours as >50 mm in Visual Analogue Scale (VAS) • To have signed voluntarily the informed consent. **Exclusion Criteria:** • Hypersensitivity to ketoprofen or to omeprazole or to another proton-pump inhibitor or to any of the excipients • Last trimester of pregnancy • History of hypersensitivity reactions to either ketoprofen or to any of the components of the formula, as well as in patients who have a history of hypersensitivity reactions to acetylsalicílic acid or any other NSAID. These reactions may include asthma attacks or any other type of allergic reaction • Gastrointestinal disorder or surgery leading to impaired drug absorption • Evidence of uncontrolled or unstable cardiac or cerebrovascular disorders that according to the investigator's opinion may be life-threatening for the subject if he/she takes part in the study • Serious blood coagulation disorder including the use of systemic anticoagulants • Positive test result for *H. pylori* at screening • Recent endoscopy showing any gastric or duodenal ulcer at least 3 mm in diameter with depth • Severe hepatic, renal and, heart failure • Patients with asthma associated to chronic rhinitis, chronic sinusitis and/or nasal polyps • Active peptic ulcer • Gastrointestinal or cerebrovascular bleeding or any other active bleeding • Alcohol consumption or drug abuse • Concomitant use with St. John's wort or atazanavir sulphate • Concomitant use of the following medications: NSAIDs including cyclooxygenase-2 selective inhibitors, salicylates, corticosteroids, disease-modifying anti-rheumatic drugs (DMARDs), antacids, Histamine H_2 receptors, Misoprostol, other PPI, Sucralphates, anticoagulants, anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs), lithium, methotrexate (at doses above 15 mg/week)

	• Laboratory values for ALT (Alanine Amino Transferase), AST (Aspartate Amino Transferase) > 2 fold the upper limit of normal at screening • Any laboratory value at screening that may be clinically significant to the investigator's opinion and may be life-threatening to the subject if he/she takes part in the study • History of malignancy, treated or untreated, the past 5 years, with the exception of successfully treated basal cell or malignancy history, treated or untreated within the last 5 years, except the successful treatment for basal cell carcinoma or squamous cell carcinoma of the skin • Participation in an investigational treatment study within 8 weeks of screening • Women with childbearing potential who do not want or cannot use a reliable contraceptive during the study • Women breast-feeding
Treatment	• One capsule of ketoprofen 200mg + Omeprazole 20mg Fixed Dose Combination (FDC) swallowed whole with food once daily, with a large glass of water. • Treatment duration: 4 weeks
Criteria for evaluation: **Efficacy:**	The effectiveness variable was evaluated as follows: • Relief of pain using a Visual Analogue Scale (VAS) • Patient's global assessment of disease activity, scored as a scale of 1 (no limitation of normal activities) to 5 (inability to carry out all normal activities)
Safety:	**Safety variables** The primary safety variable was to evaluate the incidence of dyspeptic symptoms: epigastric pain, dyspepsia, nausea at D10 The secondary safety variables were: • Incidence of dyspeptic symptoms (epigastric pain, dyspepsia, nausea) at D0, D4 and D28 • Incidence of complications (perforations, ulcers, bleeding) at D28 • Incidence of moderate to severe abdominal symptoms. • Incidence of Fecal occult blood [guaiac test] positivity at study termination (D28) • Incidence of Gastro Intestinal Adverse Events (GI AE) leading to withdrawal from the study • Adverse events reported by the patient or noted by the investigator • At each visit, arterial blood pressure and heart rate were evaluated

Statistical methods:	**Safety** Descriptive analysis of Adverse events (AE) was performed including the number and percentage of patients experiencing at least one treatment emergent adverse event (TEAE), related TEAE, serious TEAE, TEAE leading to death and TEAE leading to study drug discontinuation. The main analysis included all patients who received at least one dose of the ketoprofen/omeprazole FDC [Intent-to-treat population (ITT)]. A secondary safety analysis was performed considering patients with fix dose only. Two patients received ketoprofen/omeprazole as a free dose combination were excluded for this analysis (Modified-Intent-to-Treat Population (mITT). Incidence of dyspeptic symptoms (epigastric pain, dyspepsia, nausea) at D0, D4 and D28 were estimated only by frequency and percent of cases. **Effectiveness** • Relief of Pain [Visual Analogue Scale (VAS)] Pain decrease was evaluated using a repeated measurement analysis: Mean changes between VAS measurements from V1 (day 0) to V4 (day 28) were analyzed as main efficacy criteria. Same analysis were performed for VAS mean changes from V2 (day 4) to V3 (day 10). • Patient's global assessment of disease activity, scored as a scale of 1 (no limitation of normal activities) to 5 (inability to carry out all normal activities) was analysed using a Non-parametric Friedman test. Per-Protocol Population (PP) was defined as the population who complied with the following criteria: 1. Patients who met the inclusion criteria and do not present any exclusion criteria. 2. Patients with complete visits (including patients who withdrew from the study by adverse event or by lack of clinical efficacy). 3. Treatment compliance defined at least 80% of total administered dose. 4. Subjects who received a fixed dose of the study treatment. Safety analysis is performed on ITT and mITT populations. Effectiveness analysis is done on PP population as protocol stated, and for comparative purposes is performed in mITT population.

Results:	A total of 54 patients were included in this study in 4 centers. ITT population included 54 patients; the mITT population, 52 (2 patients were treated with a free dose combination) and the PP population 17 patients. 37 patients presented a protocol deviation (concomitant medication during study trial). For ITT population mean age was 50.5±10.85 years and 51 (94.4) % was females. 38.9% suffered from Rhumatoid Arthritis, 55.6 % of Osteoarthritis and 5.6 of Ankylosing Spondyloarthritis**.** The onset of the current episode of pain was 26.1 ±12.8 hours. 20.4 % had a previous NSAID treatment. 68.5% of patients received a concomitant treatment during the trial. Most of them received 2 or 3 medications. 15.7% received a DMAR, 7.4% a NSAIDs, 2.5% an antiulcer drug, 1.7 % an analgesic and, 1.7% a corticosteroid. There was one severe dyspepsia case as withdrawals during study. **<u>Safety results</u>** **Primary endpoint:** • Two patients (3.7% and 3.8% considering the ITT and mITT population, respectively) reported dyspeptic symptoms (epigastric pain, dyspepsia, nausea) at day 10 (visit 3). **Secondary endpoints:** • One patient (1.85% and 1.92% considering the ITT and mITT population, respectively) reported dyspeptic symptoms (epigastric pain, dyspepsia, nausea) at day 4 (visit 2). Two patients (3.7% and 3.8% considering the ITT and mITT population, respectively) reported dyspeptic symptoms (epigastric pain, dyspepsia, nausea) at day 10 (visit 3). One patient (1.85% and 1.92% considering the ITT and mITT population, respectively) reported dyspeptic symptoms (epigastric pain, dyspepsia, nausea) at day 28 (visit 4). • No complications (perforations, ulcers, bleeding) were reported. • Four patients (7.40% and 7.69% considering the ITT and mITT population, respectively) reported faecal occult blood positive. • No abdominal symptoms were reported. • One patient reported a Treatment-Emergent Adverse Event (dyspepsia) that led to discontinuation of study medication. Overall, 30 patients reported adverse events in ITT population. Possibly-related treatment-emergent adverse events were reported in 9 patients (16.67%) (Table 2). The majority of patients experienced Treatment-Emergent Adverse Events rated as mild in intensity. Faecal occult blood was observed in 15 patients (27.78 %) , and faecal occult blood considered as related to the study treatment, was observed in 4 patients (7.41%). Four patients reported two adverse events at the same time. No Serious Adverse Events were reported. There were no TEAEs that resulted in death.

All TEAE are in Table 1 (related and not related to drug medication); in Table 2 are reported only related TEAE.

Table 1. Frequency of treatment emergent adverse events during all clinical study (IIT, n=54)

Adverse Event	TEAEs (n)	TEAE (%)	Patients with at least one TEAE**	Patients with Adverse Event (%)
Faecal Occult Blood	15	33.33	15	27.78
Dyspepsia	6	13.33	5	9.26
Pharyngitis	3	6.67	2	3.70
Flu-like Syndrom	2	4.44	2	3.70
Headache	2	4.44	2	3.70
Gastroenteritis	2	4.44	2	3.70
Low Back Pain	2	4.44	1	1.85
Diarrhea	2	4.44	2	3.70
Constipation	1	2.22	1	1.85
Nausea	1	2.22	1	1.85
Dizziness	1	2.22	1	1.85
Conjunctivitis	1	2.22	1	1.85
Paresthesia	1	2.22	1	1.85
Joint Disorder	1	2.22	1	1.85
Colitis	1	2.22	1	1.85
Flatulence	1	2.22	1	1.85
Peripheral Edema (ankle)	1	2.22	1	1.85
Not classified (patient with double dose)	1	2.22	1	1.85
Total	45	100.00		

** Total patients with TEAE are 30. Only 20 patients reported 1 single TEAE, and 10 patients reported more than 1 TEAE.

Table 2. Frequency of drug related adverse events (IIT, n=54)

ADVERSE EVENT* (HOMOGENEOUS DENOMINATION)	TEAE (n)	TEAE (%)	Number of patients with at least one TEAE	Patients with adverse event (%)
Faecal Occult Blood	5	11.11	4	7.41
Constipation	2	4.44	2	3.70
Not classified (patient with double dose)	1	2.22	1	1.85
Dyspepsia	3	6.67	2	3.70

Vital signs

No clinically relevant changes from baseline to end of study were observed with respect to vital signs.

Effectiveness results

Effectiveness is reported on PP population.

Pain relief:

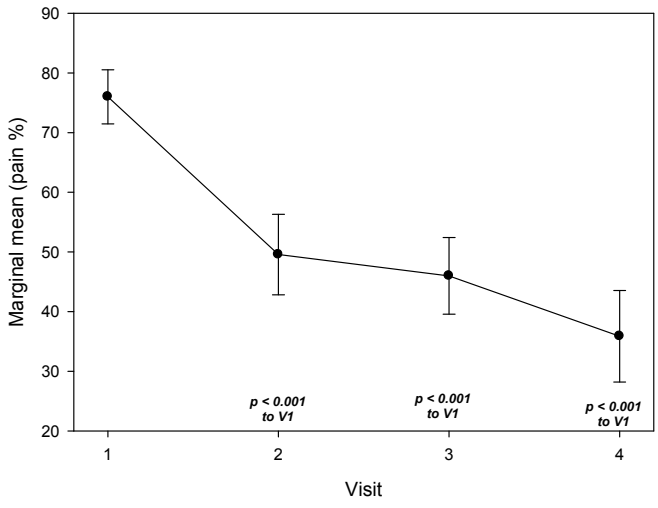
A pronounced pain decrease measured using a Visual Analogue Scale (VAS) was observed at each visit compared to the baseline (V1). VAS decrease was more pronounced from the visit 2 compared to the baseline (V1) and, the effect was maintained throughout the study (Table 3 and figure). Comparison regarding visit 1 are significant (p<0.001) under repeated measurements analysis of variance.

Table 3. Mean VAS decrease at each visit

Descriptive Statistics	Mean Pain (mm)	Standard Deviation (mm)	N*
Visit 1	76.0	18.14	16
Visit 2	49.6	26.97	16
Visit 3	46.0	25.71	16
Visit 4	35.9	30.69	16

- From 17 PP patients, only 16 were paired data (complete information for all visits)

Pillai's Trace, Wilks' Lambda, Hotelling's Trace and Roy's Largest Root are significant (p<0.001)



Effectiveness is reported on mITT population.

Pain relief:

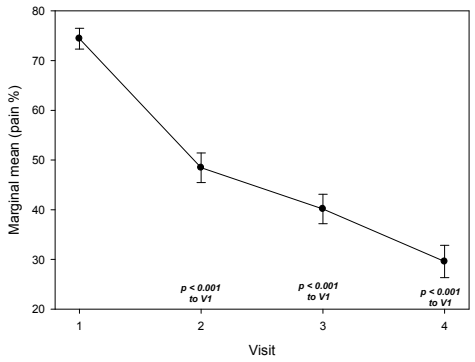
A pronounced pain decrease measured using a Visual Analogue Scale (VAS) was observed at each visit compared to the baseline (V1). VAS decrease was more pronounced from the visit 2 compared to the baseline (V1) and, the effect was maintained throughout the study (Table 4 and figure). Comparison regarding visit 1 are significant (p<0.001) under repeated measurements analysis of variance.

Table 4. Mean VAS decrease at each visit

Descriptive Statistics	Mean Pain (mm)	Standard Deviation (mm)	N*
Visit 1	74.4	14.84	50
Visit 2	48.44	21.09	50
Visit 3	40.16	21.02	50
Visit 4	29.58	22.96	50

- From 54 ITT patients, only 50 had paired data (complete information for all visits).

Pillai's Trace, Wilks' Lambda, Hotelling's Trace and Roy's Largest Root are significant (p<0.001)



Both, PP and mITT population present no differences regarding profile and pain value for different visits.

Patient Global Assessment (ITT, n=54)

66.67% of patients were considered as “completely recovered” or having experienced “Much Improvement” at Visit 4 (Table 5). Results to visit 4 are significantly different by Friedman test (p=0.011).

Table 5. Patient Global Assessment

Patient Global Assessment	VISIT 2		VISIT 4	
	N	%	N	%
Completely Recovered			5	9.30%
Much improvement	22	40.70%	30	55.60%
Low improvement	28	51.90%	14	25.90%
No Changes	3	5.60%	4	7.40%
Slightly worse	1			
Missing data			1	1.80%
Total	54	100.00%	54	100.00%

Overall, the study Ketom_L_04584 aimed to evaluate the safety, tolerability and efficacy of the combination ketoprofen / omeprazole in patients with rheumatological conditions with a previous history or who were at risk of developing NSAIDs associated benign gastric ulcers, duodenal ulcers and gastroduodenal erosions in who continued treatment with NSAIDs was necessary. It was designed to confirm that the 2 compounds administered at the same time were well tolerated and to confirm the effectiveness of the combination on symptoms related to rheumatological conditions.

A total of 54 patients were included and analysed in the ITT population. The incidence of dyspeptic symptoms at D10 (primary safety variable) was 3.7 % (ITT population). No serious adverse events were reported, and treatment emergent adverse events were reported in 30 patients, the most frequent being positive faecal occult blood test.

Regarding effectiveness of the combination ketoprofen/omeprazole, a pronounced pain relief was observed from D4 and maintained throughout the study. In addition, the patient global assessment showed a high percentage of patients recovered or improved at D28.

Date of issue:	15 October 2012