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Sponsor/company:	sanofi-aventis	**ClinicalTrials.gov Identifier:**	NCT00810121
		Study Code:	KETOP_L_03948
Generic drug name:	ketoprofen	**Date:**	24 September 2009

Title of the study:	Non-inferiority study of Bi-Profenid® 200 mg versus Bi-Profenid® 300 mg in patients presenting with pain due to closed, benign, acute post-traumatic conditions of the locomotor system or acute, non-infectious rheumatologic conditions – BIPROPAIN
Investigator(s):	Coordinating investigator : Pr Bruno RIOU Service d'accueil des Urgences Hôpital La Pitié Salpêtrière 47 Boulevard de l'hôpital 75651 PARIS cedex 13
Study center(s):	71 centers in France (70 actives centers)
Publications (reference):	Not applicable
Study period: Date first patient enrolled: 27-nov-2008 Date last patient completed: 16-jun-2009	Phase of development: IIIb
Objectives:	Primary: To demonstrate the non-inferiority of Bi-Profenid® 100 mg 2 times per day versus Bi-Profenid® 150 mg 2 times per day in patients presenting with pain due to closed, benign, acute post-traumatic conditions of the locomotor system or acute, non-infectious rheumatologic conditions, by comparing, on the one hand, changes in pain at rest intensity over the entire day, measured at the end of the day using a numeric scale (NS), over 5 days and, on the other hand, total intake of concomitant analgesics over 5 days. Secondary: • To describe concomitant analgesic treatments • To describe the time lapsed between the baseline and the use of a step I, II or III analgesic • To evaluate patient's pain relief using a Likert 4-class scale (complete or substantial relief, moderate relief; slight relief and absence of relief) at D5 • To evaluate changes in intensity of pain when moving, over the entire day, measured at the end of the day using a numeric scale, over 5 days • To evaluate the patient's overall satisfaction at the end of treatment using a 4-point Simple Verbal Scale (SVS) (very satisfied, somewhat satisfied, somewhat unsatisfied, very unsatisfied) • To evaluate the investigator's overall satisfaction at the end of the study using a 4-point Simple Verbal Scale (SVS) (very satisfied, somewhat satisfied, somewhat unsatisfied, very unsatisfied) • To compare the safety profile of the two treatments

Methodology:	National, phase IIIb, multicenter, randomised (1:1), double blind, comparative, parallel groups		
Number of patients:	Planned: 400 including 326 evaluable in Per Protocol analysis	Randomized: 409	Treated: 405
Evaluated:	Efficacy : 342 (for Per Protocol analysis)	Safety: 405	
Diagnosis and criteria for inclusion:	Patients consulting for pain due to a closed, benign, acute post-traumatic condition of the locomotor system or acute, non-infectious rheumatologic condition who do not require hospitalisation or surgery and who do not need more than 5 days of treatment.		
Investigational product: Dose: Administration:	ketoprofen (Bi-Profenid®) 100 mg 2 times per day for 5 days (formula identical to Bi-Profenid® 150 mg) Oral route		
Duration of treatment: 5 days		Duration of observation: 8 days (± 2 days)	
Reference therapy: Dose: Administration:	ketoprofen (Bi-Profenid®) 150 mg 2 times per day for 5 days Oral route		
Criteria for evaluation:			
Efficacy:	Primary criteria: The primary co-criteria of the study are pain intensity at rest over the entire day measured using a NS at the end of the day between D1 and D5 and total consumption of concomitant analgesics over 5 days. Secondary criteria ▪ Description of concomitant analgesic treatments ▪ Description of the time lapsed between the enrolment of a patient and the use of a step I, II or III analgesic. ▪ Relief of patient's pain using a Likert 4-class scale at day 5 (complete or substantial relief; moderate relief; slight relief; and absence of relief) ▪ Pain intensity when moving, over the entire day, measured at the end of the day using a NS, over 5 days ▪ Overall satisfaction of the patient at the end of treatment using a 4-point SVS (very satisfied, somewhat satisfied, somewhat unsatisfied, very unsatisfied) ▪ Overall satisfaction of the investigator at the end of the study using a 4-point SVS (very satisfied, somewhat satisfied, somewhat unsatisfied, very unsatisfied)		
Safety:	Adverse events (reported by the patient or noted by the Investigator) as well as treatment discontinuations were collected.		

Statistical methods:	Primary analysis was based on co-criteria taking into account changes in pain and total consumption of concomitant analgesics. Changes in pain: The calculation of the number of patients was performed in order to demonstrate non-inferiority, with a statistical power of 85%, in terms of changes in pain intensity (NS: 0 - 10) with the following hypotheses: ▪ Non-inferiority margin fixed at a difference of 0.5 points between the two groups for the mean of the differences over 5 days in pain intensity (DPI) in relation to the baseline visit, with a standard deviation estimated at 1.5 points. ▪ One-sided α risk of 2.5% corresponding to a two-sided confidence interval of 95% (one-sided at 97.5%); this risk was adjusted and took into account the fact that this is a primary co-criterion. ▪ 1:1 ratio. The total number of evaluable patients needed in per-protocol was 326 (163 per arm). Since the rate of exclusion from per-protocol analysis was estimated at approximately 15-20%, a total of 400 patients (200 per group) had to be included. Total consumption of concomitant analgesics: The following hypotheses have been retained after consultation with the study experts: ▪ Non-inferiority margin fixed at a difference of 1.5 g of analgesics between the two groups for total consumption of concomitant analgesics over 5 days (estimated on average at approximately 12 to 15 g of paracetamol over the entire duration of the study), with a standard deviation estimated at 3. ▪ One-sided α risk of 2.5% corresponding to a two-sided confidence interval of 95% (one-sided at 97.5%); this risk was adjusted and took into account the fact that this is a primary co-criterion (10). ▪ 1:1 ratio. Enrolling 400 patients in order to have 326 analysable patients guaranteed a statistical power of at least 95% in order to analyse consumption of concomitant analgesics. The overall statistical power needed to make a conclusion on non-inferiority was therefore at least 80% (85%, power of the first analysis x 95%, power of the second analysis = 80.75%, overall power).

Summary:	Populations analysed	Bi-Profenid® 200 mg per day	Bi-Profenid® 300 mg per day	Total
	Randomised	200 (100%)	209 (100%)	409 (100%)
	Safety	196 (98.0%)	209 (100.0%)	405 (99.0%)
	Modified ITT (mITT)	188 (94.0%)	198 (94.7%)	386 (94.4%)
	Per Protocol	170 (85.0%)	172 (82.3%)	342 (83.6%)
	Early discontinuations from the study in the treated population (Safety or ITT)			
		Bi-Profenid® 200 mg per day	Bi-Profenid® 300 mg per day	Total
	Early discontinuation from the study	10 (5.1%)	12 (5.7%)	22 (5.4%)
	Lost to follow-up	*5 (2.6%)*	*5 (2.4%)*	*10 (2.5%)*
	Adverse event	*2 (1.0%)*	*2 (1.0%)*	*4 (1.0%)*
	Insufficient efficacy	*1 (0.5%)*	*2 (1.0%)*	*3 (0.7%)*
	Refusal to continue	*1 (0.5%)*	*1 (0.5%)*	*2 (0.5%)*
	Death of patient (accident)	*0 (0.0%)*	*1 (0.5%)*	*1 (0.2%)*
	Non-eligibility	*0 (0.0%)*	*1 (0.5%)*	*1 (0.2%)*
	Disappearance of pain	*1 (0.5%)*	*0 (0.0%)*	*1 (0.2%)*
	Description of the treated population (Safety or ITT)			
	Characteristics at baseline	Bi-Profenid® 200 mg per day n=196	Bi-Profenid® 300 mg per day n=209	Total n=405
	Age (years) mean ± SD	40 ± 15	39 ± 13	40 ± 14
	Sex: Male	120 (61%)	122 (58%)	242 (60%)
	BMI (kg/m²) mean ± SD	25.0 ± 4.2	25.3 ± 4.5	25.2 ± 4.3
	Indication: rheumatologic traumatic	108 (55%) 88 (45%)	114 (55%) 95 (45%)	222 (55%) 183 (45%)
	Pain at rest mean ± SD	5.9 ± 1.4	6.2 ± 1.5	6.1 ± 1.5
	Prescription of step I analgesic	160 (82%)	173 (83%)	333 (82%)
	Median duration of treatment was 5 days in the two treatment groups and in the two populations, mITT and Per Protocol, with extremes of 1 and 7 days in the mITT population and 1 and 6 days in the Per Protocol population.			
Efficacy results	Primary co-criteria in the Per Protocol population (primary analysis)			
	Mean change between D1 and D5 in pain at rest measured using a scale of 0 to 10.	Bi-Profenid® 200 mg per day n=170	Bi-Profenid® 300 mg per day n=172	
	Mean ± Standard deviation	-2.96 ± 1.85	-2.96 ± 2.14	
	Median (Min; Max)	-2.8 (-8.0; 2.6)	-2.8 (-10.0; 4.8)	
	Intergroup difference ± Standard error	-0.00 ± 0.22		
	95% CI of the intergroup difference	[-0.43; 0.43]		
	The non-inferiority of Bi-Profenid® 200 mg per day versus Bi-Profenid® 300 mg per day is demonstrated for this criterion because the upper limit of the 95% CI is less than the non-inferiority threshold fixed at 0.5			

	Total consumption of concomitant analgesics between D1 and D5 (g)	Bi-Profenid® 200 mg per day n=170	Bi-Profenid® 300 mg per day n=172
	Mean ± Standard deviation Median (Min; Max)	4.23 ± 5.58 2 (0; 20)	4.85 ± 6.04 2 (0; 20)
	Intergroup difference ± Standard error 95% CI of the intergroup difference	-0.61 ± 0.63 [-1.85; 0.62]	
	The non-inferiority of Bi-Profenid® 200 mg per day versus Bi-Profenid® 300 mg per day is demonstrated for this criterion because the upper limit of the 95% CI is less than the non-inferiority threshold fixed at 1.5g.		
	Primary co-criteria in the mITT population (robustness analysis)		
	Mean change between D1 and D5 in pain at rest measured using a scale of 0 to 10.	Bi-Profenid® 200 mg per day n=188	Bi-Profenid® 300 mg per day n=198
	Mean ± Standard deviation Median (Min; Max)	-2.86 ± 2.06 -2.80 (-8.0; 5.0)	-2.79 ± 2.30 -2.80 (-10.0; 7.0)
	Intergroup difference ± Standard error 95% CI of the intergroup difference	-0.06 ± 0.22 [-0.50; 0.37]	
	The non-inferiority of Bi-Profenid® 200 mg per day versus Bi-Profenid® 300 mg per day is demonstrated for this criterion because the upper limit of the 95% CI is less than the non-inferiority threshold fixed at 0.5.		
	Total consumption of concomitant analgesics between D1 and D5 (g)	Bi-Profenid® 200 mg per dayd n=188	Bi-Profenid® 300 mg per day n=198
	Mean ± Standard deviation Median (Min; Max)	4.69 ± 5.99 2 (0; 20)	5.14 ± 6.24 2 (0; 20)
	Intergroup difference ± Standard error 95% CI of the intergroup difference	-0.44 ± 0.62 [-1.67; 0.78]	
	The non-inferiority of Bi-Profenid® 200 mg per day versus Bi-Profenid® 300 mg per day is demonstrated for this criterion because the upper limit of the 95% CI is less than the non-inferiority threshold fixed at 1.5g.		
Efficacy results	Analysis of secondary criteria did not detect a statistically significant difference or clinically significant difference between Bi-Profenid® 200 mg per day and Bi-Profenid® 300 mg per day, in the Per Protocol population or in the mITT population, for all of the criteria: ▪ use of an analgesic (Per Protocol: p=0.663 - mITT: p=0.736), ▪ time lapsed until analgesic use (Per Protocol: p=0.894 - mITT: p=0.734), ▪ mean change in pain when moving (Per Protocol: p=0.27 - mITT: p=0.49 - median = -1.80 points in the two groups and the two populations), ▪ patient relief (Per Protocol: p=0.100 - mITT: p=0.122), ▪ patient's overall satisfaction (Per Protocol: p=0.908 - mITT: p=0.995), ▪ investigator's overall satisfaction (Per Protocol: p=0.524 - mITT: p=0.451).		

Safety results:	The frequency of adverse events was similar with the two treatments in terms of all of the treatment emergent adverse events (TEAE) (Bi-Profenid® 200 mg per day: 21.4%; Bi-Profenid® 300 mg per day: 19.6%), TEAEs linked to treatment by the investigator (Bi-Profenid® 200 mg per day: 15.3%; Bi-Profenid® 300 mg per day: 17.2%), TEAEs responsible for early discontinuation of treatment (Bi-Profenid® 200 mg per day: 3.6%; Bi-Profenid® 300 mg per day: 5.3%) or non-emergent events occurring during the post-treatment period (1% in each group). Treatment related TEAE were expected events, mainly gastrointestinal events (Bi-Profenid® 200 mg per day: 14.8%; Bi-Profenid® 300 mg per day: 15.3%), particularly stomach ache (Bi-Profenid® 200 mg per day: 8.7%; Bi-Profenid® 300 mg per day: 9.6%). Gastrointestinal disorders were responsible for most of the premature discontinuations of treatment (Bi-Profenid® 200 mg per day: 4 patients out of 7 discontinuations; Bi-Profenid® 300 mg per day: 11 patients out of 11 discontinuations). No serious adverse event occurred during the treatment period. The death of a patient in a car accident that occurred during the post-treatment period was not related to treatment with Bi-Profenid® 300 mg per day. Heart rate, systolic blood pressure and diastolic blood pressure remained stable during the study.
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