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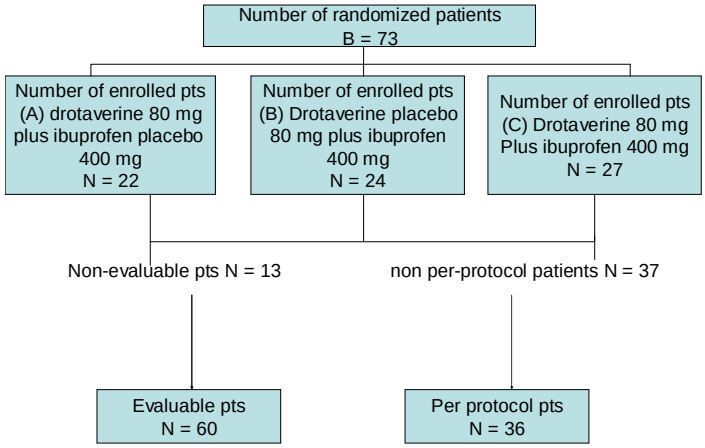
Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00292747
		Study Code:	L_9134
Generic drug name:	drotaverine	**Date:**	12 November 2008

Title of the study:	Comparison of the efficacy and tolerability of drotaverine 80 mg or ibuprofen 400 mg administered alone with their combination for the treatment of primary and secondary dysmenorrhea. Randomized, double-blind, double-dummy, comparative, multicentre parallel group phase IV trial		
Investigator(s):	Investigators: Dr. János Demeter MD.PhD. Head of Department Of Gynecology and Obstetric of "Szent Rókus" Hospital Tel: 26-62-561 Dr. Péter Székely MD, Department Of Gynecology of "Városi Egészségügyi Szolgálat" Tel: 06-52-414-808 Principal investigator and coordinator: Prof. Zoltán Papp M.D. D.Sc., Head of Department Of Gynecology and Obstetric I. of University Semmelweis Tel: 266-04-73		
Study center(s):	Department Of Gynecology and Obstetric of "Szent Rókus" Hospital Department Of Gynecology and Obstetric of Városi Egészségügyi Szolgálat Number of active centers and the name of countries: 2, Hungary		
Publications (reference):	NA		
Study period: Date first patient enrolled: 25/05/2005 Date last patient completed: 28/02/2006		Phase of development: IV	
Objectives:	To show that the combination of drotaverine 80mg and ibuprofen 400 mg is more effective and well-tolerated as drotaverine 80 mg and ibuprofen 400 mg administered alone		
Methodology:	multicentre, comparative, randomized, placebo-controlled, double-blind, double-dummy, parallel groups		
Number of patients:	Planned: 480	Randomized: 73	Treated: 73
Evaluated:	Efficacy/Pharmacodynamics: 60	Safety: 73	

	Distribution of the patients evaluated 
Diagnosis and criteria for inclusion:	• Women suffering from primary or secondary dysmenorrhea • Women aged between 18 and 45 years • History of at least 6 months of dysmenorrhea, with presence of moderate to severe pain in each of the last 3 cycles • With regular menstrual cycles (25-35 days) • Using an adequate barrier contraception method (except for virgins) • Able and willing to give a written informed consent
Investigational product: Dose: Administration:	 • Group A: drotaverine 80 mg + ibuprofen 400mg placebo • Group B: drotaverine 80mg placebo + ibuprofen 400 mg • Group C: drotaverine 80 mg + ibuprofen 400 mg Oral
Duration of treatment: Treatment period: 3 whole days (72 hours). Dose: 9 doses /treatment period, maximum 3 doses daily (= 3 x 2 tablets/day). The patient should take the first dose at the onset of the menstrual cramp, but within 24 hours before the bleeding	**Duration of observation:** one menstrual cycle/pts
Reference therapy: Dose: Administration:	 Rescue medication will be permitted after one hour of administration of the first dose of the trial medication, provided that the intensity of pain was different from 0 (“none”) or 1 (“mild”) on the categorical scale, or at any time later if necessary Oral

Criteria for evaluation:	
Efficacy:	Pain intensity was rated by patients on a 4-point categorical scale (0=none, 1=mild, 2=moderate, 3=severe) at baseline and 0.5, 1, 2, 4 and 6 hours after the first dose and 0, 0,5 and 2 hours after the fourth dose Primary: – Reponse rate in each treatment arm. The response rate is defined as follows: the proportion of patients having pain intensity score 0 or 1 at hour 2 after the first drug intake. Secondary: - the weighted sum of pain intensity differences over the first 6-hour observation period after the first drug intake - the weighted sum of pain intensity differences over the first 2-hour observation period after the fourth drug intake - the proportion of patients requiring (permitted) rescue medication - the proportion of dropouts (taking forbidden rescue medication) - pain intensity differences at each timepoint (compared to the baseline, hour 0 at the first drug intake) - patients' global assessment of efficacy
Safety:	– Occurrence of adverse events – Patient's overall global assessment of tolerability (excellent, good, fair, poor) – Laboratory parameter

Statistical methods:	With a significance level of 50% and a power of 80%, 426 evaluable patients were needed. Assuming a dropout rate of 12%, 480 patients have to be enrolled in the study. When 200 patients completed the study, an interim analysis for sample size reassessment will be performed. Data will remain blinded towards the sponsor and towards the investigators. Since the clinically relevant difference on which the sample size evaluation relies (=15%) will remain unchanged, no adjustment in the significance level is needed. The response rates in the three arms will be compared by a global chi-square test and differences between response rates and their 90% confidence intervals will be computed. The weighted sum of pain intensity differences over the first 6-hour observation period after the first drug intake and the weighted sum of pain intensity differences over the first 2-hour observation period after the fourth drug intake will be assessed by ANOVA accounting for the fixed effects of treatment, centre and treatment x centre interaction. The proportion of patients requiring rescue medication will be compared by chi-square test. Pain intensity differences at each time-point (compared to the baseline, hour 0 at the first drug intake) will be assessed by Kruskal-Wallis tests applied at each time-point separately. The patients' global assessment of efficacy and tolerability will be assessed by a Kruskal-Wallis test. Safety analysis will be done on the safety population, for all patients included in the study. The proportion of patients reporting adverse events will be compared by a chi-square test. Adverse events will be tabulated by severity, relationship to the study medication and outcome. The mean percent changes from baseline and their 95% confidence intervals was computed for each laboratory parameter. The study was early discontinued at 16/04/2007 because of slow enrollment, therefore no interim report was done.

Summary:	
Efficacy results:	Primary efficacy endpoint The primary efficacy endpoint was the response rate in each treatment arm. The response rate is defined as follows: the proportion of patients having pain intensity score 0 or 1 at hour 2 after the first drug intake. The response rates in the three arms were compared by a global chi-squared test and differences between response rates and their 90 % confidence intervals were computed. The primary efficacy parameter was analyzed for both the evaluable /ITT and the per protocol patients. *Primary efficacy results for evaluable protocol* Table 1 represents the response rate for evaluable patients. The condition of the chi-squared test does not realized, because 3 cells (50 %) have expected counts less than 5. The main reason for this effect, that the sample number (number of patients) is too small in this study. Therefore the result of the chi-square test has to be interpreted carefully because of the very low sample size. Result of Fisher's test is that there was no significant difference between the group A (drotaverine 80 mg and ibupofren 400 mg placebo), group B (drotaverine 80 mg placebo and ibupofren 400 mg) and group C (drotaverine 80 mg and ibupofren 400 mg), because probability is lower than must be considering the 90 % significance level (p=0.167, Table 2). The relationship between the group variable and response rate was measured by Phi, Cramer's V and contingency coefficient (Table 3). The low values of the measures show that there was weak relationship between the treatment arms and response rate. Table 4 summarizes response rates for evaluable patients. Table 5 shows the differences and the 90% confidence intervals for differences of response rates in treatment arms calculated in evaluable protocol. Table 1. Response rate: descriptive statistics by treatment group (evaluable protocol)

			Pain intensity after two hours the first drug intake		
			None or mild pain	Moderate or severe pain	Total
Treatment group	A	Count	12	6	18
		Expected Count	14,4	3,6	18,0
		% within Treatment group	66,7%	33,3%	100,0%
	B	Count	15	4	19
		Expected Count	15,2	3,8	19,0
		% within Treatment group	78,9%	21,1%	100,0%
	C	Count	21	2	23
		Expected Count	18,4	4,6	23,0
		% within Treatment group	91,3%	8,7%	100,0%
Total		Count	48	12	60
		Expected Count	48,0	12,0	60,0
		% within Treatment group	80,0%	20,0%	100,0%

Table 2. Response rate: global chi-squared test and Fisher's exact test (evaluable protocol)

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)	Point Probability
Pearson Chi-Square	3,850[a]	2	,146	,155		
Likelihood Ratio	3,987	2	,136	,182		
Fisher's Exact Test	3,798			,167		
Linear-by-Linear Association	3,786[b]	1	,052	,078	,040	,024
N of Valid Cases	60					

a. 3 cells (50,0%) have expected count less than 5. The minimum expected count is 3,60.

b. The standardized statistic is -1,946.

Table 3. Relationship between treatment arms and response rate (evaluable protocol)

		Value	Approx. Sig.	Exact Sig.
Nominal by Nominal	Phi	,253	,146	,155
	Cramer's V	,253	,146	,155
	Contingency Coefficient	,246	,146	,155
N of Valid Cases		60		

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

Table 4. Responder rate (evaluable protocol)

Treatment group	Responders(/N)	Responder rates
A	12/18	66.7%
B	15/19	78.9%
C	21/23	91.3%

Table 5. Responder rate differences (evaluable protocol)

Comparison	% Differences	90% CI
C vs. A	24.6	(4.0, 45.3)
C vs. B	12.4	(-5.8, 30.5)

Primary efficacy results for per protocol

Table 6 represents the response rate for per protocol patients.
The condition of the chi-squared test does not realized, because 3 cells (50 %) have expected counts less than 5. The main reason for this effect, that the sample number (number of patients) is too small in this study. Therefore the result of the chi-square test has to be interpreted carefully because of the very low sample size.
Result of Fisher's test the test is that there is significant difference between the group A (drotaverine 80 mg and ibupofren 400 mg placebo), group B (drotaverine 80 mg placebo and ibupofren 400 mg) and group C (drotaverine 80 mg and ibupofren 400 mg), because possibility is lower than must be considering the 90 % significance level (p=0.029 < 0.5, Table 7).
The relationship between the group variable and response rate was measured by Phi, Cramer's V and contingency coefficient (Table 8). The medium values (~0.4) of the measures show that there was moderate relationship between the treatment arms and response rate for per protocol patients.
Table 9 summarizes response rates for per protocol patients. Table 10 shows the differences and the 90% confidence intervals for differences of response rates in treatment arms calculated in per protocol.

Table 6. Response rate: descriptive statistics by treatment group (per protocol)

			Pain intensity after two hours the first drug intake		
			None or mild pain	Moderate or severe pain	Total
Treatment group	A	Count	4	5	9
		Expected Count	7,0	2,0	9,0
		% within Treatment group	44,4%	55,6%	100,0%
	B	Count	9	1	10
		Expected Count	7,8	2,2	10,0
		% within Treatment group	90,0%	10,0%	100,0%
	C	Count	15	2	17
		Expected Count	13,2	3,8	17,0
		% within Treatment group	88,2%	11,8%	100,0%
Total		Count	28	8	36
		Expected Count	28,0	8,0	36,0
		% within Treatment group	77,8%	22,2%	100,0%

Table 7. Response rate: global chi-squared test and Fisher's exact test (per protocol)

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)	Point Probability
Pearson Chi-Square	7,726[a]	2	,021	,018		
Likelihood Ratio	6,957	2	,031	,051		
Fisher's Exact Test	6,433			,029		
Linear-by-Linear Association	5,301[b]	1	,021	,028	,020	,015
N of Valid Cases	36					

a. 3 cells (50,0%) have expected count less than 5. The minimum expected count is 2,00.

b. The standardized statistic is -2,302.

Table 8. Relationship between treatment arms and response rate (per protocol)

		Value	Approx. Sig.	Exact Sig.
Nominal by Nominal	Phi	,463	,021	,018
	Cramer's V	,463	,021	,018
	Contingency Coefficient	,420	,021	,018
N of Valid Cases		36		

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

Table 9. Response rate (per protocol)

Treatment group	Responders(/N)	Responder rates
A	4/9	44.4%
B	9/10	90.0%
C	15/17	88.2%

Table 10. Response rate differences (per protocol)

Comparison	% Differences	90% CI
C vs. A	43.8	(13.7, 73.9)
C vs. B	-1.8	(-22.0, 18.5)

According to the protocol, the study was powered to detect a difference of 15% between the combination of the two drugs and the other two treatment arms. The attained difference between the combination and drotaverine was even higher than this (24.6% for all evaluable subjects, see in Table 5 and 43.8% for the per protocol population, see in Table 10), and it was statistically significant (based on the 90% CI of the difference between response rates). However, no statistically significant difference was found between the combination of the two drugs and ibuprofen, response rates were of similar magnitude (for the per protocol subjects response rates were even slightly higher for ibuprofen than for the combination, see in Table 10 the value -1.8).

Weighted sum of pain intensity differences over the first 6-hour observation period after first drug intake

Weighted sum of pain intensity differences were computed as the sum of pain intensity differences weighted by the length of the time interval since the previous observation. The weighted sum of pain intensity differences over the first 6-hour observation period after the first drug intake were assessed within an ANCOVA framework accounting for the fixed effect of treatment and baseline pain score (pain score before the first drug intake) as a covariate. ANCOVA p-values were: $p=0.503$ for the treatment effect and $p<0.001$ for the baseline effect.

There was no statistically significant difference (at level 5%) between the treatment groups. However, based on the 95% confidence intervals of the least-squares means, there was a statistically significant decrease from baseline in all the three treatment groups.

	Weighted sum of pain intensity differences over the first 2-hour observation period after fourth drug intake The weighted sum of pain intensity differences over the first 2-hour observation period after the fourth drug intake were assessed within an ANCOVA framework accounting for the fixed effect of treatment and baseline pain score (pain score before the fourth drug intake) as a covariate. ANCOVA p-values were: p=0.279 for the treatment effect and p=0.176 for the baseline effect. There was no statistically significant difference (at level 5%) between the treatment groups. However, based on the 95% confidence intervals of the least-squares means, there was a statistically significant decrease from the pain score before the fourth drug intake in all the three treatment groups. Pain intensity differences at each time-point were assessed by Kruskal-Wallis tests applied at each time-point separately There are no significant difference between treatment arms A, B and C considering pain intensity differences at each time-point There are no significant difference between treatment arms A, B and C, considering global assessment of efficacy or tolerability.
Safety results:	No SAE was reported. Adverse events were at 11 from the all 73 patients (A-6, B-1, and C-4). There was no significant difference between the groups considering adverse events (Chi-square and Fisher's exact test). Mean changes of laboratory parameters were similar in the most cases in arms. Adverse event are listed bellow in the safety population*. The condition of the chi-squared test does not realized, because 3 cells (50 %) have expected counts less than 5. But Fisher' exact test was executed. The result of test is that there is no significant difference between the group A (drotaverine 80 mg and ibupofren 400 mg placebo), group B (drotaverine 80 mg placebo and ibupofren 400 mg) and group C (drotaverine 80 mg and ibupofren 400 mg), because possibility is higher than must be considering the 95 % confidence interval (p=0.098 >0.05). All adverse events in the safety population (case number in brackets) *Headache(2), dizziness(2), vertigo(2), nausea(4), vomitus, stiching feel in right breast and in the lower abdomen(1), vision disturbancies(1), sleepiness(1), stomach ache(1), diarhoea (1), tiredness (1)
Date of report:	30/10/2008