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Sponsor/company:	sanofi-aventis	ClincialTrials.gov Identifier:	NCT00556179
		Study Code:	LACTO_L_02399
Generic drug name:	Lactic Acid	Date:	21/Dec/2009

Title of the study:	Local, national (Brazil), multicenter, open label, non-controlled, phase IV study of Lactic acid (Dermayd® Femina), in women at reproductive age, to prevent recurrence of Bacterial Vaginosis, during three months, after standard treatment with metronidazol. (Code: LACTO_L_02399)		
Investigator(s):	José Antônio Simões/Luis Bahamondes. Address: R. Vital Brasil, 250 – Barão Geraldo - São Paulo - Brazil Zip Code: 13024-500		
Study center(s):	One center – Brazil. It was planned a multicenter study with two sites, however one of them gave up before it would be opened.		
Publications (reference):			
Study period: Date first patient enrolled: 28-Sep-2007 Date last patient completed: 15-Dec-2008		Phase of development: Phase IV	
Objectives:	Primary: The purpose of this study was to evaluate the recurrence rate of Bacterial Vaginosis up to ninety days of daily use of Dermacyd® Femina, initiated after end of the standard treatment with metronidazole. Secondary: To determine the rate of vulvovaginal candidiasis during the Dermacyd® Femina use. Evaluation and comparison between the scores reported by the patients in the Quality of Life Self Evaluation Questionnaire before the beginning of the Dermacyd® Femina use and after the end of the use. Safety was evaluated by adverse events reported by the patients or noted by the investigators.		
Methodology:	Single-center study, non-comparative and open label.		
Number of patients:	Planned: 122	Randomized: NA Included: 123	Treated: 92
Evaluated:	Efficacy: 84	Safety: 92	

Diagnosis and criteria for inclusion:	Women in reproductive age (≤ 50 years old) with confirmed diagnosis of BV, defined as fulfilled at least three of the following criteria: (a) homogeneous vaginal discharge without inflammation of the vagina or vulva, (b) vaginal pH >4.5, (c) positive Whiff test, and (d) "clue cells" in more than 20% of the epithelial cells in a fresh vaginal exam. Also, Nugent score >4 at vaginal bacterioscopy stained by Gram. After the BV diagnosis, oral metronidazole 500mg should be administered twice a day during seven days. After that, all women with cure of the BV were instructed to initiate Dermacyd® Femina use.
Investigational product: Dose: Administration:	Lactic acid (Dermacyd® Femina) The patients should be applying small quantity (between 7.5 to 10mL) of the product in the external genitalia until obtaining foam and, after that, rinse the region abundantly. Once a day.
Duration of treatment: Ninety days. *The Dermacyd® Femina use should be started after the end of BV treatment with metronidazole (500mg, twice a day, for seven days).*	Duration of observation: 90 days.
Criteria for evaluation:	
Efficacy:	Recurrence rate of Bacterial Vaginosis during the use of Dermacyd® Femina at each visit: 30, 60 and 90 days after the treatment started. Rate of vulvovaginal candidiasis during the Dermacyd® Femina use. Difference between the scores reported by the patients in the Quality of Life Self Evaluation Questionnaire before the beginning of the Dermacyd® Femina use and after the end of the use. The questionnaire of self-evaluation is a five items questionnaire applied in the form of visual analogue scale (VAS) to the patients that reached cure of BV after the standard treatment with metronidazole. The questionnaire was applied before the beginning of the Dermacyd® Femina use and after the end of the use. The zero-scale represented "unsatisfied with the results" and ten-scale "full satisfied with the results". The questions were as follow: 1) level of comfort at the genital region, 2) malodorous at external genitalia, 3) comfort at sexual relationship, 4) satisfied or not regarding intimae hygiene, and 5) self-esteem.
Safety:	Adverse events reported by the patient or noted by the investigator.
Statistical methods:	It was calculated the proportion of the patients with BV recurrence at each visit: 30, 60 and 90 days after the starting of Dermacyd® Femina use and it was built the corresponding 95% Confidence Interval. It was considered a successful treatment if it was not observed recurrence of BV through the 90 days of follow-up. It was also analyzed the rate of vulvovaginal candidiasis during the treatment with Dermacyd® Femina and the corresponding 95% Confidence Interval. The results of the Quality of Life Self Evaluation Questionnaire were presented as mean, standard deviation (SD), median and range for each one of the five items. The analysis included a paired t-Test to compare the values before and after the treatment. The level of significance adopted was 0.05. All analysis performed followed the principle of Intention to Treat. The efficacy parameters were analyzed for all patients who used Dermacyd® Femina at least once and had at least one available evaluation for BV recurrence after the beginning of the treatment. All patients who used Dermacyd® Femina at least once were included in the SAFETY Population.

Summary:	Between 28-Sep-2007 and 05-Sep-2008, 123 patients were enrolled to the study. The mean age of the participants was 32.0 (SD: 7.2) years, with a range from 18 to 50 years old. From the total of the patients enrolled, 67 (54.5%) women were white, 31 (25.2%) were black and 24 (20.3%) black-Caucasian bi racial. The body mass index (BMI; kg/m2) of the patients enrolled was 26.5 ± 5.4 with a range from 16.8 to 41. Thirteen (10.6%) patients presented some medical associated condition and the three more prevalent was blood hypertension (2.4%), bronchitis (2.4%) and epilepsy (1.6%). Regarding contraceptive practice at the time of the study, 82 (66.7%) were users of a copper intrauterine device (IUD , 62,6%) or a levonorgestrel-releasing intrauterine system (LNG-IUS; 4.1%), 12 (9.8%) were users of male condom, 19 (15.4%) were users of combined oral (8,1%) or injectable contraceptives (7.3%), 7 (5.7%) performed male or female sterilization and the other 3 (2.4%) declared the usage of other contraceptive methods. Concerning diagnosis at inclusion, from the total of 123 patients enrolled, 117 (95.1%) presented vaginal discharge observed at the gynecological exam; whereas the vaginal pH >4.5 was observed in 121 (98.4%) of the patients, "clue cells" at the fresh exam in all the 123 patients, positive Whiff test in 119 (96.8%) of the subjects, and Nugent score >4 in all the patients. Consequently, all the patients fulfilled at least three of the criteria for BV diagnosis at enrollment and all of them were instructed to initiate the metronidazole oral treatment. After the end of the treatment with metronidazole (Visit V0), 100 (81.3%) patients showed negative results for BV, 9 (7.3%) presented no cure and the other 14 (11.4%) were not evaluated (12 due to lost of follow up, one due to protocol violation (Diabetes Mellitus) and the other one because consent withdrawal. However, only 92 (74.8%) women initiated the use of Dermacyd® as 5 (4.1%) were lost to follow up, 2 (1.6%) presented candidiasis and one presented an adverse event: gastric intolerance to metronidazole. The flow chart presented below describes the distribution of patients enrolled, cured with metronidazole and evaluable for BV recurrence: 123: enrolled [Visit V-1] ↓ 12: lost to follow up / 1:Protocol violation (DM) / 1: consent withdrawal / 9: no cure of BV 100: Cure with metronidazole [Visit V0] ↓ 5: Lost to follow up/ 8: Candidiasis / 1: Adverse event + Candidiasis / 2: No evaluation for BV was performed 84: Evaluable for BV after 30 days of treatment with Dermacyd [Visit V1] ↓ 16: BV recurrence / 3: Lost to follow up / 2: Candidiasis / 1: protocol violation (use of vaginal cream) 62: Evaluable for BV after 60 days of treatment with Dermacyd [Visit V2] ↓ 15: BV recurrence / 3: Candidiasis / 1: Lost to follow up / 1: Protocol violation (pregnancy) 42: Evaluable for BV after 90 days of treatment with Dermacyd [Visit V3]

Efficacy results:

The table below shows the rate of Bacterial Vaginosis recurrence at the three visits and the respective 95% Confidence Interval ($CI_{95\%}$).

From the total of patients that used Dermacyd® Femina and was evaluated to BV during the period of the study, 34 (50.5%) presented Bacterial Vaginosis recurrence, with a 95% confidence interval associated of 30.0% to 51.0%.

Table 1: Recurrence of Bacterial vaginosis trough the study.

Visit	Number of evaluable patients	BV Recurrence N (%)	$CI_{95\%}$
V1	84	16 (19.0%)	[10.6% - 27.4%]
V2	62	15 (24.6%)	[13.8% - 35.4%]
V3	42	3 (7.3%)	[0.7% - 15.3%]
Ever	84	34 (40.5%)	[30.0% - 51.0%]

The evaluation of the scores reported by the patients in the Quality of Life Self Evaluation Questionnaire before the beginning of Dermacyd® Femina use (Visit V0) and after the end of the use

(Visit V3) are showed at Table 2, as mean ± standard deviation, Minimum and Maximum values. It was only compared the 42 women who completed the three visits scheduled after the beginning of the treatment

It is also showed at Table 2 the mean ± standard deviation, Minimum and Maximum values for the difference between the scores at Visit V0 and Visit V3 and the value of the paired t-Test statistic used to compare the two visits, with the respective p-value associated to. The comparison showed that for all items of the questionnaire, as well for the sum of them, it was detected a significant improvement at the end of the treatment.

Table 2: Quality of Life Self Evaluation Questionnaire

Items	Visit V0 (N=42)	Visit V3 (N=42)	Visit V0 – Visit V3	p-value*
Level of comfort	8.1 ± 1.9 Min: 3.0 Max: 10.0	9. 2 ± 1.1 Min: 5.8 Max: 10.0	-1.08 ± 1.59 Min:- 5.5 Max: 2.7	t = -4.41 p<0.0001
Malodorous at external genitalia	8.5 ± 1.9 Min: 3.5 Max: 10.0	9.4 ± 1.1 Min: 4.0 Max: 10.0	-0.89 ± 1.81 Min: - 6.1 Max: 2.5	t = -3.19 p=0.0027
Comfort at sexual relationship	8.1 ± 2.4 Min: 0.5 Max: 10.0	9.3 ± 0.8 Min: 7.2 Max: 10.0	-1.29 ± 2.04 Min: - 8.0 Max: 1.2	t = -3.98 p=0.0003
Satisfied with the intimae hygiene	8.4 ± 2.1 Min: 1.5 Max: 10.0	9.3 ± 1.3 Min: 2.6 Max: 10.0	-0.90 ± 1.48 Min: - 5.0 Max: 1.2	t = -3.94 p=0.0003
Self-esteem	8.5 ± 1.9 Min: 1.0- Max: 10.0	9.4 ± 0.7 Min: 6.8 Max: 10.0	-0.90 ± 1.71 Min: - 7.0 Max: 2.5	t = -3.40 p=0.0015
Sum of the scores	41.4 ± 7.5 Min: 25.7 Max: 50.0	46.6 ± 3.9 Min: 29.8 Max: 50.0	-5.19 ± 5.75 Min: - 19.1 Max: 3.0	t = -5.71 p<0.0001

* Paired t-Test.

From the total of 123 patients enrolled, 10 (8.1%) presented candidiasis before the beginning of Dermacyd® Femina use.

From the 92 patients that have used the product, 12 (13.0%) patients presented candidiasis. Five (5.4%) of then after the beginning of he Dermacyd® Femina use, with a 95% Confidence Interval associated of CI95%: [0.8% ; 10.0%].

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<td>Safety results:</td>
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The Table 3 summarizes the number of patients that reported adverse events and the number of adverse events reported during the study.
From the 92 patients that have used Dermacyd® Femina at least once during the study, 40 (43.5%) patients have reported 54 Adverse events.
Nine (9.8%) patients have presented 11 events considered as related to Dermacyd® Femina as follow: candidiasis, erythema, hyperemia, irritation and itching vulval.
It was reported a serious adverse event by two patients, both not related to Dermacyd® Femina. One patient presented invasive carcinoma of uterine collum and another one inguinal cutaneous abscess.

Table 3: Patients reporting any adverse event.
<table>
<tr><th>Adverse event</th><th>Nº of treated patients (N=92)</th><th>Nº of events</th></tr>
<tr><td>Any</td><td>40 (43.5%)</td><td>54</td></tr>
<tr><td>Related to Dermacyd® Femina</td><td>9 (9.8%)</td><td>11</td></tr>
<tr><td>Serious</td><td>2 (2.2%)</td><td>2</td></tr>
<tr><td>Serious and Related to Dermacyd® Femina</td><td>-</td><td>-</td></tr>
</table>

One patient became pregnancy during the study. The contraceptive method reported by this patient at enrolment period was male condom.
The most frequent adverse events were: candidiasis, reported by 12 patients (13.0%); lumbago and vulval itching, both reported by 3 (3.26%) patients; hypogastric pain, pelvic pain, vulval excoriation and urinary infection were presented each one in 2 patients (2.8%).
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