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Sponsor/company: sanofi-aventis	clinicaltrials.gov Identifier: NCT00331994
	Study Code: PM_L_0161
Generic drug name: Bacillus clausii spores	Date: 17/Jul/2009

Title of the study:	Efficacy evaluation of Enterogermina, 2 billion *Bacillus clausii* spores, on eradication of small intestinal bacterial overgrowth: a randomised, parallel-group, open study.		
Investigator(s):	Prof. Antonio Gasbarrini		
Study center(s):	Istituto di Patologia Speciale Medica e Semeiotica Medica Università Cattolica del Sacro Cuore Policlinico A. Gemelli		
Publications (reference):	None		
Study period: Date first patient enrolled: 26 April 2006 Date last patient completed: 31 July 2008	Phase of development: IV		
Objectives:	<u>Primary objective:</u> To assess the efficacy of *Bacillus clausii* in the eradication of SIBO (small intestinal bacterial overgrowth) vs Metronidazole, 30 days after the end of treatment. <u>Secondary objectives</u>: To assess the efficacy of *Bacillus clausii* vs Metronidazole in avoiding recurrence of SIBO, 90 days after the end of the treatment. To assess the efficacy of *Bacillus clausii* vs Metronidazole in improving IBS-related symptoms. To assess the efficacy of *Bacillus clausii* vs Metronidazole in the satisfactory relief of overall IBS symptoms and of abdominal discomfort or pain. To assess the efficacy of *Bacillus clausii* vs Metronidazole in improving IBS quality of life.		
Methodology:	Single centre, randomised, parallel-group, two-grouped comparative open study. Phase IV study. Group 1: Enterogermina Group 2: Metronidazole		
Number of patients:	Planned: 312	Randomized: 250 (125 per group)	Treated: 230

Evaluated:	ITT: 230 (109 Enterogermina; 121 Metronidazole), PP: 172 (75 Enterogermina; 97 Metronidazole)	Safety: 230 (109 Enterogermina; 121 Metronidazole)	Pharmacokinetics: NA
Diagnosis and criteria for inclusion:	Adult male and female subjects with SIBO and diagnosis of irritable bowel syndrome according to Rome II criteria and able to maintain their usual diet and lifestyle during the course of the study.		
Investigational product: Dose: Administration:	Enterogermina (*Bacillus clausii* spores) Vial containing 2×10^9 spores of antibiotic-resistant *Bacillus clausii* 3 Enterogermina vials/day for one month oral		
Duration of treatment: one month (Enterogermina) one week (Metronidazole)		Duration of observation: between 97 and 120 days, depending on the length of the treatment	
Reference therapy: Dose: Administration:	Metronidazole 250 mg tablet 3 Metronidazole tablets/day for one week oral		
Criteria for evaluation:			
Efficacy:	The <u>primary efficacy variable</u> was the eradication rate of SIBO 30 days after the end of treatment, as measured by the glucose breath test and the lactulose breath test. Eradication was defined as H_2 excretion ≤10 ppm and/or methane excretion ≤3 ppm over the baseline value within 2 h (GBT) and within 4 h (LBT). A patient was considered responder if both H_2 excretion and methane excretion were classified negative by the Investigator. <u>Secondary efficacy variables</u> included: - Recurrence of SIBO according to breath test performed 90 days after the end of the treatment - Assessment of IBS-related symptoms using the diary; patients recorded the presence and severity of several IBS-related symptoms daily in the diary for the entire treatment period and for one month post-treatment. Patients were asked to characterize their abdominal discomfort or pain, bloating, stool frequency and stool consistency - Satisfactory relief of overall IBS symptoms and abdominal discomfort or pain - Improvement of quality of life, using the IBS-QOL questionnaire		
Safety:	- Adverse Events (AEs) recording - Vital signs and physical examinations		

Statistical methods:	All the efficacy data were described for both ITT and PP populations. Complete descriptive analysis of patients' disposition, including number of screened patients, randomized patients, no. of patients who completed the study, no. of discontinued patients and primary reason of the discontinuation. Demographic and screening/baseline characteristics as well as treatment exposure and compliance were described for the safety population. Primary efficacy variable: The primary efficacy variable was the eradication rate of SIBO 30 days after the end of treatment, measured by the breath test. The primary variable was analyzed by means of two-sided Chi-square test at α level of 0.05. The analysis was also stratified by age and thyroid disease and data were processed by the Cochran-Mantel-Haenszel test. Secondary efficacy variables: The eradication rate of SIBO 90 days after the end of treatment was processed by a two-sided Chi-square test. An additional stratified analysis by age and thyroid disease was performed as for the primary endpoint. Transition tables were generated to highlight shifts vs. baseline of breath test results, 30 and 90 days after the end of treatment. Proportion of relapses at day 90 was analyzed by treatment on patients cured at day 30; a transition table day 90 vs baseline and chi-square test to compare relapse rates among treatments. The IBS-QOL questionnaire total score summarized at each time point was analyzed by means of analysis of variance model for repeated measures. The overall IBS related symptoms relief and the discomfort/pain was evaluated between treatment groups by means of Chi square test, at each time point. Safety data: The number of all adverse events and the number of patients with adverse events was shown by treatments as well as statistics on relationship to study drug, seriousness and severity, reporting absolute and relative frequencies. Vital signs and physical examination were described by visit and by treatment.

Summary:	
Efficacy results:	Analysis of primary efficacy variable The eradication rate of SIBO was significantly higher in the Metronidazole group than in Enterogermina group in both the ITT population (54.5% vs. 28.4%, p-value=0.0003) and in the PP population (62.9% vs. 33.3%, p-value=0.0001). An exploratory analysis was conducted only in patients positive at H_2 test at baseline. The eradication rate was still significantly lower in the Enterogermina group than in Metronidazole group (26.6% vs. 52.1%, p-value=0.0002). A stratification by age classes, as defined by the sample quartiles, and by thyroid disease confirmed these results. In the ITT population, the relative risk of success (Enterogermina vs. Metronidazole) ranged from a minimum of 0.46 for the age class 38-47 years to a maximum of 0.70 for the class 18-27 years. The Cochran-Mantel-Haenszel (CMH) test showed an overall significant p-value (p-value=0.0002), and the Breslow-Day test did not reject the hypothesis of a common relative risk through age classes. A similar trend was observed stratifying by thyroid disease, with Metronidazole being superior to Enterogermina in both subjects with and without thyroid disease (CMH p-value=0.0001). Analyses of secondary efficacy variables The results of the eradication rate of SIBO 90 days after the end of treatment confirmed the results observed 30 days after the end of treatment: Enterogermina vs Metronidazole rates of success were 26.6% vs. 50.4% in the ITT population (p-value=0.0004) and 25.3% vs. 56.7% in the PP population (p-value < 0.0001). Stratification by age and thyroid disease supported these results. A higher rate was observed for Enterogermina (41.9% vs. 15.2%, p-value=0.0054) on the relapse rate of SIBO 90 days after the end of treatment. Metronidazole had a worse total score than Enterogermina at baseline of quality of life through the IBS-QOL questionnaire. A trend toward a gradual improvement was evident, from baseline through last visit, approximately of the same degree for both treatments. An analysis of covariance (ANCOVA) model was employed to investigate the differences between treatments at the time points 30 and 90 days after treatment end, including baseline score as covariate. Neither 30 days nor 90 days after the end of treatment a treatment difference could be detected, while baseline covariate was significant. At the end of treatment a higher percentage of IBS symptoms relief was reported in the Enterogermina group for both IBS symptoms (14.7% vs. 1.7%, p-value=0.0055) and abdominal pain (13.7% vs. 3.4%, p-value=0.0306). Thirty days after the end of treatment the percentage distribution reversed, turning in favour of Metronidazole: in fact the percentages of the two classes summed up to 31.3% (Metronidazole) vs. 11.5% (Enterogermina) for IBS symptoms (p-value=0.0007) and to 30.4% (Metronidazole) vs. 11.5% (Enterogermina) for abdominal pain (p-value=0.0008). At the last visit no difference among treatments came out.

Safety results:	The percentage of patients with adverse events were low for both treatments (5.5% for Enterogermina vs. 6.6% for Metronidazole). No serious adverse events were reported. Two patients per group had adverse events of grade 3 (severe intensity): in the Enterogermina group bronchopneumonia and respiratory tract infection, none of them drug related or leading to drug discontinuation; in the Metronidazole group migraine and vomiting, the latter being drug related and leading to drug discontinuation. One more case of vomiting was considered related to Metronidazole. The two patients classified as discontinued due to adverse events in the Enterogermina group, were judged as protocol violators regarding the main reason for discontinuation, despite the action taken for these events was 'study treatment permanently discontinued'; actually, the adverse events they complained of (i.e. bronchopneumonia and respiratory tract infection) required the usage of not allowed drugs (antibiotics) and this was the main reason why they discontinued the study.
Date of report:	11June 2009