These results are supplied for informational purposes only.

Prescribing decisions should be made based on the approved package insert in the country of prescription

Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00457353
		Study Code:	ENTER_L_01486
Generic drug name:	Bacillus clausii multi-antibioresistant spores	**Date:**	31 December 2008

Title of the study:	A phase III, controlled, open-label, randomized, parallel group, multicentric, comparative study to assess the efficacy and safety of oral rehydration therapy (ORT) in combination with spores of Bacillus clausii (Enterogermina™) versus ORT alone, administered for 5 days in the treatment of acute diarrhea in children STUDY CODE: ENTER_L_01486
Investigator(s):	Dr. Keya R. Lahiri (Coordinating Investigator) Seth G.S. Medical College & K.E.M. Hospital, Parel, Mumbai-400012, India
Study center(s):	6 centers in India
Publications (reference):	Nil

Study period: Date first patient enrolled: 02-03-2007 Date last patient completed: 26-12-2007	Phase of development: III

Objectives:	Primary objective • To demonstrate the efficacy of treatment with ORT in combination with Bacillus clausii probiotic strain (Enterogermina™) as compared to treatment with ORT alone, for a period of 5 days, in reducing the duration of acute diarrhea in Indian children. Secondary objectives • To evaluate the clinical safety of Enterogermina™ in acute diarrhea in children • To demonstrate the effect of Enterogermina™ on ▪ stool frequency ▪ stool consistency ▪ number of vomiting episodes ▪ hydration in children suffering from acute diarrhea
Methodology:	Phase III, controlled, open-label, randomized, parallel group, multicentric, comparative study

Number of patients:	Planned: 264	Randomized: 264	Treated: 264
Evaluated:	255	Safety: 255	
Diagnosis and criteria for inclusion:	Infants and children aged between 6 months to 5 years and suffering from acute diarrhea of less than 48 hours duration attending the out patients department and whose parent / legal guardian* gave a written informed consent for participation in the study were included in the study. [*Parent: means a child's biological or adoptive parent. Legal Guardian: is defined as an individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care, when general medical care includes participation in research. A guardian also means an individual who is authorized to consent on behalf of a child to participate in research.]		
Investigational product: Dose: Administration:	Treatment arm: ORT + spores of *Bacillus clausii* (Enterogermina™) Control arm : ORT alone Treatment arm: ORT (as per Investigator's recommendations) + Enterogermina™ - 2 vials/day; for a period of 5 days Control arm: ORT alone (as per Investigator's recommendations); for a period of 5 days Zinc supplement dose of 20mgm/day was given additionally for both the treatment arms as per standards recommended by Indian Academy of Pediatrics/WHO/UNICEF Oral		
Duration of treatment: 5 days		Duration of observation: 10 days	

Criteria for evaluation:	
Efficacy: Safety:	Primary endpoint: Duration of diarrhea, as counted from the first intake of the investigational product up to the first appearance of a loose stool followed by two consecutive normal stools. Secondary endpoints: • Mean number of stools per day • Effect on consistency of stools • Occurrence of vomiting episodes per day after enrolment • Physical evaluation done at V1 and V2 (including body weight) • Adverse events reported by the patient/subject or noted by the investigator • Parents' overall global assessment of tolerability (excellent, good, fair, poor) at the end of the treatment period
Statistical methods:	Four data sets were defined: the Randomized population that included all the patients with a treatment number, the Safety Population which included all the randomized patients who received at least one treatment dose, the Intent-to-Treat (ITT) Population which included all the randomized patients who were evaluated at least once during the treatment period (after inclusion) and the Per-Protocol (PP) Population which included the randomized patients with at least one evaluation after inclusion and without major deviations at inclusion or during the study. Demographic characteristics and baseline parameters were described on the ITT population. The main efficacy criterion - the duration of the diarrhea – was compared between treatment arms on the ITT population by a log-rank test (Kaplan-Meier survival analysis). Secondary analyses on the main criterion consisted of the comparison of duration of diarrhea (Student's t-test) on patients who had no more diarrhea at the end of treatment and on patients who did not reach the event (end of diarrhea), setting the duration of the diarrhea to 5 days (120 hours). Supportive analysis of the primary criterion was performed on the PP data set.
Summary:	255 patients aged 6 months-5 years were evaluated for treatment of diarrhea. The patients were randomized into two groups where control group received ORT alone and treatment group received ORT + Enterogermina™. Both the groups were given Zinc supplement as a standard therapy as recommended by WHO Mean frequency of diarrhea episodes per day at inclusion was 6.2±2.1 and 6.1±2.2 in the E+O and O groups, respectively. The duration of diarrhea in hours at inclusion was 26.5±11.3 and 26.9±12.2 in the E+O and O groups, respectively.

Efficacy results:	Though the mean duration of diarrhea was less in the E + O group (48.6± 38.2 hours), the difference of 7.5 hr was not statistically significant as compared to the O group (56.1±40). On similar analysis carried out in the two subgroups formed on the basis of the age. o In 6 months to 2 years age of children, the trend tended to favor the E + O group (50.4±38.2) over the O group (58.1± 40.9) in terms of lesser duration of diarrhea. The difference in the two groups was not statistically significant o In 2 years to 5 years age of children, the trend tended to favor the E+O group (43.2±38.2) over the O group (51.9± 38.2) in terms of lesser duration of diarrhea. The difference in the two groups was not statistically significant The mean number of stools until recovery was higher in the O group (8.6± 6.5) than E + O group (7.4± 6.5). The difference in the two groups was not statistically significant. On comparing the consistency of stools in the two groups on different days, it was seen that the decrease in the proportion of patients with watery or loose stools was higher for E + O group (Watery (N) = 57, 31, 14, 4, 3 and 3, Loose (N) = 61, 66, 53, 35, 25 and 14) than O group (Watery (N) = 52, 34, 18, 6, 5 and 2, Loose (N) = 64, 62, 63, 44, 26 and 18) at day1, day2, day3, day4, day5 and day 6, respectively. The difference between the groups was not statistically significant. There was a statistically significant fall in the mean number of vomiting episodes in the E + O group (0.2± 0.7, p-value = 0.0020) on day 3 while it was seen on day 4 in the O group (0.2± 0.6, p-value = 0.0085) by comparing with day1. No patient in the E + O group was suffering from dehydration at visit 2, while 1 patient (0.8%) in the O group was suffering from some dehydration at visit 2. Secondary Analyses: Mean duration of diarrhea between the two groups in children between 6 months to 24 months for the Per Protocol population was: ORT + Enterogermina (N=93) was 50.8±38.7 hours and for the ORT was (N=84) 57.9±41.3 hours. This difference favored the E Group but was not statistically significant (p=0.24). Mean duration of diarrhea between the two groups in children between 2 years to 5 years for the Per Protocol population was: ORT + Enterogermina (N=29) was 38.5±35.9 hours and for the ORT was (N=40) 51.9±38.2 hours. This difference favored the E Group but was not statistically significant (p=0.14)
Safety results:	There was no significant increase in the incidence of adverse events in the E + O group as compared to the O group. (E + O group =46; O group = 41). Most of the AEs seen during the study were of GI origin and majority of AEs were documented as unrelated to study medications. There were no serious adverse events in the study. The overall tolerability for Enterogermina seems to be excellent, As around 69% patients (n=90) in the E group rated the treatment to be excellent. Rest of the parents (n=35) rated the efficacy to be good and none parent rated the efficacy to be poor. Only the first dose received was rated as “poor” by 2 parents. No subsequent dose was rated poor by the parents of the subjects.
Date of report:	29-07-2008