*These results are provided for informational purposes only.*
*Prescribing decisions should be made based on the approved package insert in the country of prescription.*

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| **Sponsor / Company**: Sanofi<br>**Drug Substance**: Cassia Fistula + Senna Alexandrina Miller | **Study Identifier**: NCT00931853<br>**Study Code**: SENCA_L_04392 |
| **Title of the study:** | National study, phase III, parallel, double blind, placebo comparative and randomized to evaluate the therapeutic efficacy and tolerability of the combination Naturetti® (Cassia Fistula + Senna Alexandrina Miller) in the Chronic Functional Constipation |
| **Study center(s):** | 1 Brazilian active site |
| **Study period:**<br>Date first patient enrolled: 15-Sep-2010<br>Date last patient completed: 28-Dec-2011 | |
| **Objectives:** | **Primary endpoint:**<br>To evaluate the clinical efficacy of the composition Cassia Fistula + Senna Alexandrina Miller (jelly sugar free) during a treatment period of 30 days, in patients with Chronic Functional Constipation (CFC), considering the following criteria:<br>- Frequency of evacuation during the treatment and follow-up period;<br>- Consistency of stools during the treatment and follow-up period according to the Bristol Scale;<br>- Global improvement of Chronic Functional Constipation (CFC) defined as an increasing in the frequency of evacuation together with a decreasing in the consistency of the stools (classification according to the Bristol Scale predominantly with value> 2);<br><br>**Secondary endpoints:**<br>- Number of days without evacuation;<br>- Proportion of evacuation with: pain, strain, incomplete sensation, blocked stools and usage of manual maneuvers to facilitate the defecation;<br>- Proportion of patients who adhere to the recommendations about the diet rich in fibers, suitable Water Intake and physical exercise;<br>- Proportion of patients who had used the rescue medication;<br>- Level of constipation improvement, according to the patient evaluation;<br>- Adverse events occurrence. |

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| **Design:** | Unicentric, randomized (1:1), double blind, parallel, placebo controlled study comprising three periods as below:<br><br>*Screening Period*<br>V0: Screening visit;<br>- Diagnosis of CFC (according to the ROME III criteria)<br>- Delivery of Instructions about the need of a diet rich in fibers, suitable water Intake and physical exercise for CFC improvement.<br><br>*Pre-treatment Period (10 days)*<br>V1: Randomization visit (D0);<br>- Checking of the persistence of the CFC diagnosis (according to the ROME III criteria) even with the adoption of the recommendations about diet and physical exercise.<br>- Randomization<br><br>*Treatment Period (30 days)*<br>V2: After 15 days of treatment;<br>V3: After 30 days of treatment; (end of treatment)<br><br>*Follow-up Period (30 days)*<br>V4: About 30 days after treatment completion<br><br>During all study periods, the patients should fulfill a diary with information about: number of evacuation, consistency type of stools according to the Bristol scale, evacuation with pain, strain, incomplete sensation, blocked and manual maneuvers, adherence to diet and exercises recommendation and study medication and rescue medication intake.<br><br>During the Treatment and Follow-up period it was allowed the use of rescue medication (Simple Herbal Medicines, laxative, enhancer of fecal material containing as active ingredient Plantago ovata Forsk) whenever the patient remained without evacuation for more than four days or in case of abdominal discomfort caused by constipation. The administration recommended was one sachet before each main meals (breakfast, lunch and dinner), dissolved in 250ml of water. When the rescue medication is used in the treatment phase, the study medication (active or placebo) should not be interrupted.<br><br>In case of treatment interruption due to an excessive number of daily evacuations or due to adverse events, the treatment could be reintroduced after three days without evacuation or after the spontaneous remission of the Adverse Events (AEs).<br><br>Both treatments to be compared, active and placebo of Naturetti® , were stored in identical packaging, indistinguishable, with exactly the same size and shape, with content of identical color, appearance and flavor. | | |
| **Number of patients:** | Planned: 96<br>(48 per treatment arm) | Randomized: 96<br>(48 per treatment arm) | Treated: 96 |
| **Evaluated:** | Efficacy : 84 | Safety: 96 | Pharmacokinetics: NA |

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| **Diagnosis and criteria for inclusion:** | - Diagnosis of Chronic Functional Constipation according to the ROME IIII criteria;<br>- Majority of the stool classified as type 1 or 2 according to the Bristol Stool Scale;<br>- age ≥ 18 and ≤ 59 years old;<br>- No previous history or current neurological and/or metabolic disorder and/or endocrine disorder;<br>- No constipation caused by previous surgery;<br>- No intestinal obstruction including colon/rectum cancer ;<br>- No Irritable bowel syndrome or inflammatory bowel disease;<br>- No continuous treatment with the following: analgesics, anticholinergic (antihistamines, antispasmodics, antidepressants, antipsychotics) iron supplements or aluminium, opiates, antihypertensive, calcium channel blockers and ganglion blocker; |
| **Investigational product:** | Naturetti® (Cassia Fistula + Senna Alexandrina Miller) jelly sugar free<br>(vial contained a net weight of 260 grams and a measuring spoon) |
| Dose: | daily administration of one spoon (5 g) during 30 days |
| Administration: | Oral |
| **Duration of treatment:** 30 days | **Duration of observation:** 70 days<br>About 10 days (pre-treatment phase) + 30 days (treatment period) + 30 days (follow-up period) |
| **Reference therapy:** | Placebo of Naturetti® (Cassia Fistula + Senna Alexandrina Miller)<br>(vial contained a net weight of 260 grams and a measuring spoon) |
| Dose: | daily administration of one spoon (5 g) during 30 days |
| Administration: | Oral |

| Criteria for evaluation: | |
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| **Efficacy:** | ***Primary:***<br>- Mean of Evacuation Frequency (MEF): calculated by the number of days with evacuation in the treatment period divided by the number of days of the treatment period (the same rational was applied for the follow-up period);<br>- Mean of stools' Consistency (MCS): calculated, for the treatment period and for the follow-up period, according to the Bristol Scale: Types 1-2 indicate constipation, with 3 and 4 being the ideal stools, and, 5, 6 and 7 tending towards diarrhoea;<br>- Global Improvement of Constipation (GIC): a patient should be considered as with a GIC in case of an increasing in the MEF in the treatment period in comparison to the pre-treatment period together with a MCS classification according to the Bristol Scale predominantly with value> 2, in the treatment period.<br><br>***Secondary:***<br>- Number of days without evacuation: it was considered as the greater range of days without evacuation in the treatment period, according to the patient diary.<br>- Proportion of evacuation with pain;<br>- Proportion of evacuation with strain;<br>- Proportion of evacuation with incomplete sensation;<br>- Proportion of blocked stools;<br>- Proportion of manual maneuvers to facilitate defecation;<br>- Proportion of subjects who adhere to the diet recommendation;<br>- Proportion of the patients who had used rescue medication;<br>- Level of constipation improvement, according to the patient evaluation:<br>1 - Much better, 2 - Better, 3 - Unchanged; 4 – Worse; 5 – Much Worse. |
| **Safety:** | Adverse events reported by the patient or noted by the investigator. |

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| **Statistical methods:** | Sample Size rational<br>48 patients should be recruited in order to obtain 33 evaluable patients by treatment group. It was assumed as an expected proportion of patients with Global Improvement of Constipation (GIC) of 60% in the treatment group and of 30% in the control (placebo) group at the end of treatment period. It was adopted a statistical power of 80%, a significance level of 5% (one-sided) and a drop-out rate of 30%.<br><br>Methodology<br>All randomized patients who had used at least one dose of the study drugs were considered in the Intent-to-treat (ITT) population. From this total, the patients who completed all study periods, without any major protocol violation were considered in the Per-Protocol (PP) population. Major protocol violations were defined independently of the identification of the treatment. The efficacy and safety analyses were conducted based on the ITT population and the analysis involving the primary objective were also performed based on PP population.<br>The demographic variables of continuous nature were described separately for the two treatment groups by the mean, standard deviation and range and the comparison of the treatment groups was indicated by the p-value of the t-Student Test. The discrete demographic variables were summarized in frequency tables and the comparison of the treatment groups was based on the p-value of the Chi-square or Fisher's test, depending on the frequency of the events.<br>All tests applied were performed using SPSS (version 15.0). It was adopted a statistical significance level of 5%.<br><br>Primary analysis<br>It was applied a t-Student test to compare the study groups, Placebo and Active, about the Mean of Evacuation Frequency (MEF) and Mean of stools' Consistency (MCS) in the Pre-treatment, Treatment and Follow-up periods.<br>The Chi-square test, the Relative Risk (RR) and the respective 95% Confidence Interval ($CI_{95\%}$) were calculated to compare the study groups, for ITT and PP Populations, about the proportion of patients who reached:<br>- An increasing in the MEF in the treatment period in comparison to the pre-treatment;<br>- A MCS classification according to the Bristol Scale predominantly with value > 2 in the treatment period;<br>- Global Improvement of Constipation (GIC): increasing in the MEF in the treatment period in comparison to the pre-treatment period together with a MCS classification according to the Bristol Scale predominantly with value> 2, in the treatment period.<br>For GIC it was also calculated the Confidence Interval $CI_{95\%}$ for the difference between GIC in the Active Group and in the Placebo Group. |

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| **Statistical methods (continuation):** | Secondary analysis<br>The parameters of continuous nature were described separately for the two treatment groups by the mean, standard deviation and range. The comparison of the treatment groups was indicated by the p-value of the t-Student Test. Discrete variables were summarized in frequency tables and the comparison of the treatment groups was based on the p-value of the Chi-square test. The analyses were performed for the ITT population.<br>A Logistic Regression model using SAS version 9.1 for ITT population during the treatment period was applied, to compare the groups about the proportion of patients with Global Improvement of Constipation (GIC) taking into account the use of rescue medication and the adherence to the recommendations about diet and physical exercises. It was adopted in the model:<br>- Response variable<br>• GIC (Yes or No);<br>- Predictor variables<br>• Number of days of rescue medication usage;<br>• Number of days with adherence to the recommendations about diet and physical exercises.<br>• Treatment Group: Placebo and Active. |

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| **Summary:** | Patients enrollment<br>Between 15-Sep-2010 and 29-Dec-2011, 117 patients were enrolled to the study. From this total, 21 (17.9%) were screening failure. A total of 96 patients, as planned, were randomized to the study treatments: 48 (50.0%) to the Active Group and 48 (50.0%) to the Placebo Group.<br>Demographic data<br>The age of patients at time of inclusion ranged from 24 to 46 years, with a mean age of 41.1 (SD=9.7) years for Placebo Group and from 19 to 58 years, with a mean age of 40.3 (SD=10.4) years for Active Group. There was no statistically significant difference between them (p-value=0.700).<br>About patients' ethnicity, most of patients were Caucasian: 35 (72.9%) and 44 (91.7%) patients, respectively, in the Placebo Group and in the Treatment Group. The other patients, in both groups, were black.<br>Most of the patients, in both groups, were women: 46 (95.8%) in the Placebo Group and 47 (97.9%) in the Active Group.<br>Study Populations<br>**117** patients screened<br>↓ 21 patients: Screening Failure<br>**96** patients randomized (48 per Group)-**ITT Intent to Treat Population (Safety)** [1]<br>V2 not performed:<br>2 Placebo: 1 Consent withdrawal / 1 Lost to follow up<br>2 Active: 1 Consent withdrawal / 1 Pregnancy<br>↓<br>V3 not performed:<br>5 Placebo: 2 Consent withdrawal / 1 Lost to fup at V2 / 2 AEs [2]<br>3 Active: 1 Consent withdrawal / 2 Lost to fup<br>**84** patients (41 Placebo; 43 Active) - **ITT Population (all evaluation at V3 available)**<br>↓ 3 Placebo: 1 Consent withdrawal at V2 / 2 Non-adherence to the study treatment [3]<br>4 Active: 1 Consent withdrawal at V3 / 2 Lost to fup at V3 / 1 Non-adherence to study treatment (but patient was followed until the end of study)<br>**77** patients (38 Placebo; 39 Active) [4] - **PP Per Protocol Population**<br>[1] Patients received at least one dose of study medication<br>[2] Stomach pain, nausea and reflux<br>Abdominal pain, abdominal edema, meteorism and vomiting<br>All of then considered as related to the study medication.<br>[3] The patient received less than 80% of the planned study medication<br>[4] Two patients of Active Group had used less than 80% of the planned study medication (70% and 77.8%). They were maintained in the PP population as both had interrupted the treatment due to an episode of diarrhea and the treatment was reintroduced after three days. |

**Summary (continuation):**

Study Period

From the 96 patients enrolled to the study, 84 (87.5%) were followed until the end of treatment period (Table 1).

**Table 1. Time of Follow-up for the patients enrolled to the study**

| Visits - Study Period | Placebo N=48 | Active N=48 |
|---|---|---|
| V1 Randomization visit | 48 (100.0%) | 48 (100.0%) |
| V2 (15 days) Treatment period | 46 (95.8%) | 46 (95.8%) |
| V3 (30 days) Treatment period | 41 (85.4%) | 43 (89.6%) |
| V4 (60 days) Follow up period | 33 (79.2%) | 40 (83.3%) |

Number of days of study medication intake – ITT population.

Comparing the number of days with study medication intake between study groups (Placebo and Active) there was not found a statistically significant difference between them (Table 2).

**Table 2. Number of days with intake of the study medication - ITT**

| Number of days | Treatment period | |
|---|---|---|
| | Placebo N=41 | Active N=43 |
| Mean (S.D) | 28.8 (2.2) | 28.0 (4.3) |
| Median | 30 | 30 |
| Min-Max | 19 - 30 | 5 - 30 |
| p-value | 0.115 | |

Concomitant medication not allowed by the protocol

The patients who had used medication not allowed by the protocol were maintained in the study population as they had used the medications sporadically (not in a continuously administration) and for a short period (1 to 4 days). In addition, none of the patients in the PP population had used any medication considered as with laxative effect.

In the Placebo group two patients had used non-allowed medications during the treatment period: atenolol (1 and 2 days), glycerol (1 day), ibuprofen (1 day) and sodium docusate (1 day). In the Active group, 7 patients had used non-allowed medications: scopolamine (1 and 2 days), codeine (1 day) and ibuprofen (3 and 4 days).

**Efficacy results:**

**Primary endpoints**

- Mean of Evacuation Frequency (MEF)

The mean number of evacuation in the pre-treatment period was similar for both study groups: 0.40 (SD=0.28) for Placebo group and 0.36 (SD=0.24) for Active group. It was not detected difference between them (p=0.483) (Table 3).

In the treatment period, it was observed a statistically significant difference between the groups (p=0.004). The mean number of evacuation were higher in the Active group 0.89 (SD=0.39) than in the placebo one0.64 (SD=0.40) (Table 3).

**Table 3. Mean of evacuation Frequency by period and Group – ITT**

| MEF | Pre-treatment period | | Treatment period | |
|---|---|---|---|---|
| | Placebo N=41 | Active N=43 | Placebo N=41 | Active N=43 |
| Mean (S.D) | 0.40 (0.28) | 0.36 (0.24) | 0.64 (0.40) | 0.89 (0.39) |
| Median | 0.3 | 0.3 | 0.5 | 0.8 |
| Min-Max | 0.1 - 1.3 | 0.1 - 1.5 | 0.2 - 1.6 | 0.1 - 2.1 |
| p-value | 0.483 | | 0.004 | |

- Mean of stools' Consistency (MCS) according to the Bristol Scale

The mean number of evacuation classified according to the Bristol Scale as type>2 in the pre-treatment period was similar for both study groups: 0.21 (SD=0.31) for Placebo group and 0.20 (SD=0.29) for Active group. It was not detected difference between them (p=0.879) (Table 4).

In the treatment period, it was observed a statistically significant difference between the groups (p=0.0003). The mean number of evacuation classified as type>2 were higher in the Active group 0.66 (SD=0.31) than in the placebo 0.41 (SD=0.30) (Table 4).

**Table 4. Number of evacuations classified as type >2 by period and Group - ITT**

| MCS | Pre-treatment period | | Treatment period | |
|---|---|---|---|---|
| | Placebo N=41 | Active N=43 | Placebo N=41 | Active N=43 |
| Mean (S.D) | 0.21 (0.31) | 0.20 (0.29) | 0.41 (0.30) | 0.66 (0.31) |
| Median | 0.0 | 0.0 | 0.4 | 0.7 |
| Min-Max | 0.0 - 1.0 | 0.0 - 1.0 | 0.0 - 1.0 | 0.0 - 1.0 |
| p-value | 0,879 | | 0.0003 | |

**Efficacy results (continuation):**

- Global Improvement of Constipation (GIC) – ITT Population

For the ITT Population it was observed a statistical significant difference between study groups for the three parameters (Table 5), proportion of patients who reached:

- Increasing in the MEF in the treatment period in comparison to the pre-treatment;

- MCS classification according to the Bristol Scale predominantly with value >2 in the treatment period;

- Global Improvement of Constipation (GIC): increasing in the MEF in the treatment period in comparison to the pre-treatment period together with a MCS classification according to the Bristol Scale predominantly with value> 2, in the treatment period.

For MEF, about 81% of the patients in the Active group and 58% of the patients in the placebo group had a mean number of evacuations higher in the treatment period than in the pre-treatment one (p=0.0145), leading to a Relative Risk (Active/Placebo) of 1.393 and a respective $CI_{95\%}$ of [1.058; 1.834] (Table 5).

For MCS, in the Active group, about 60 % of the patients, and in the Placebo group, about 28% of the patients, had evacuations predominantly classified as type>2 in the treatment period (p=0.0010), leading to a Relative Risk (Active/Placebo) of 2.231 and a respective $CI_{95\%}$ of [1.32997; 3.743] (Table 5).

The proportion of patients who presented GIC was 58.3% in the Active group and 18.8% in the Placebo group (p<0.0001). The difference between the proportion of patients with Global Improvement of Constipations between groups Active and Placebo was 39.5% with an associated $CI_{95\%}$ of [20.0%; 59.5%] (Table 5).

The Relative Risk indicated an increasing in the GIC for Active group in relation to the Placebo of 3.111, with an associated $CI_{95\%}$ of [1.648; 5.874] (Table 5).

**Table 5 – Primary Efficacy parameters – ITT Population**

| *ITT* | Placebo (N=48) | Naturetti (N=48) | $X^2$ ; p-value | RR (Naturetti/Placebo) ; $CI_{95\%}$ |
|---|---|---|---|---|
| MEF | 28 (58.3%) | 39 (81.2%) | 5.9784 ; p=0.0145 | 1.3929 ; [1.0580 ; 1.8338] |
| MCS | 13/41 (27.8%) | 29/43 (60.4%) | 10.8360 ; p=0.0010 | 2.2308 ; [1.3294 ; 3.7432] |
| GIC | 9 (18.8%) | 28 (58.3%) | 15.8754 ; p<0.0001 | 3.1111 ; [1.6477 ; 5.8741] |
| Difference between Groups (GIC): 58.3% - 18.8% = 39.5% - $CI_{95\%}$: [20.0% ; 59.5%] | | | | |

**Efficacy results (continuation):**

- Global Improvement of Constipation (GIC) – PP Population

The results found in the PP population were very similar to those observed in the ITT population. It was detected a statistical significant difference between study groups for the three parameters (Table 6).

The difference between the proportion of patients with Global Improvement of Constipations between groups Active and Placebo for PP Population was 35.2% with an associated $CI_{95\%}$ of [12.9%; 48.1%]. The Relative Risk indicated an increasing in the GIC for Active group in relation to the Placebo of 2.215, with an associated $CI_{95\%}$ of [1.277; 2.654] (Table 6).

**Table 6 – Primary Efficacy parameters – PP Population**

| *PP* | Placebo | Active | $\chi^2$; p-value | RR (Activei/Placebo); $CI_{95\%}$ |
|---|---|---|---|---|
| MEF | 26/38 (68.4%) | 35/39 (89.7%) | 5.316; p=0.0211 | 1.3116; [1.031 ; 1.669] |
| MCS | 15/38 (39.5%) | 26/39 (66.7%) | 5.717; p=0.0168 | 1.689; [1.075 ; 2.654] |
| GIC | 11/38 (28.9%) | 25/39 (64.1%) | 9.555; p=0.0020 | 2.215; [1.277 ; 2.654] |
| Difference between Groups (GIC): 64.1% - 28.9% = 35.2% - CI95%: [12.9%; 48.1%] | | | | |

- Mean of Evacuation Frequency (MEF) in the follow-up period

Comparing the treatment and follow-up periods, for the Active group it was found a statistically significant difference in the MEF (p=0.012). The mean of evacuation frequency was greater in the treatment period (0.89; SD=0.39) than in the follow-up period (0.70; SD=0.30). For the Placebo group there was no found a statistically significant difference (p=0.655) between the two study periods (Table 7) for MEF.

**Table 7. Mean of evacuation Frequency in the follow-up period – ITT**

| MEF | Placebo (N=41) | | Active (N=43) | |
|---|---|---|---|---|
| | Treatment period | Follow-up period | Treatment period | Follow-up period |
| Mean (S.D) | 0.64 (0.40) | 0.70 (0.40) | 0.89 (0.39) | 0.70 (0.30) |
| Median | 0.5 | 0.6 | 0.8 | 0.7 |
| Min-Max | 0.2 - 1.6 | 0.2 - 2.3 | 0.1 - 2.1 | 0.2 - 1.3 |
| p-value | 0.655 | | 0.012 | |

**Efficacy results (continuation):**

- Mean of stools' Consistency (MCS) according to the Bristol Scale in the follow-up period

Comparing the treatment and follow-up periods, for the Active group it was found a statistically significant difference in the MCS (p=0.043). The mean number of evacuations classified according to the Bristol Scale as type>2 was greater in the treatment period (0.66; SD=0.31) than in the follow-up period (0.50; SD=0.40). For the Placebo group there was no found a statistically significant difference (p=0.493) between the two study periods (Table 8) for MCS.

**Table 8. Number of evacuations classified as type >2 in the follow-up period - ITT**

| MCS | Placebo (N=41) | | Active (N=43) | |
|---|---|---|---|---|
| | Treatment period | Follow-up period | Treatment period | Follow-up period |
| Mean (S.D) | 0.41 (0.30) | 0.50 (0.40) | 0.66 (0.31) | 0.50 (0.40) |
| Median | 0.4 | 0.4 | 0.7 | 0.4 |
| Min-Max | 0.0 - 1.0 | 0.0 - 1.0 | 0.0 - 1.0 | 0.0 - 1.0 |
| p-value | 0.493 | | 0.043 | |

**Secondary endpoints**

- Number of days without evacuation.

About the mean days without evacuation (Table 9) it was observed a statistically significant difference (p=0.048) between Placebo and Active groups, respectively with mean and SD of 3.6 (SD=2.3) and 2.7 (SD=1.8).

**Table 9 – Number of days without evacuation – Treatment period – ITT Population**

| Number of days without evacuation | Treatment period | |
|---|---|---|
| | Placebo N=41 | Active N=43 |
| Mean (S.D) | 3.6 (2.3) | 2.7 (1.8) |
| Median | 3.0 | 2.0 |
| Min-Max | 0 - 9 | 0 - 9 |
| p-value | 0.048 | |

- Proportion of evacuation with pain.

About the proportion of evacuation with pain (Table 10) in the treatment period, it was observed in the Placebo group a mean (0.3; SD=0.3) greater than the mean observed in the Active group (0.2; SD=0.3), but without statistically significant difference (p=0.138).

**Efficacy results (continuation):**

**Table 10 – Proportion of evacuation with pain – Treatment period – ITT Population**

| Proportion of evacuation with pain | Treatment period | |
|---|---|---|
| | Placebo N=41 | Active N=43 |
| Mean (S.D) | 0.3 (0.3) | 0.2 (0.3) |
| Median | 0.3 | 0.1 |
| Min-Max | 0.0 - 1.0 | 0.0 - 1.0 |
| p-value | 0.138 | |

- Proportion of evacuation with strain.

About the proportion of evacuation with strain (Table 11), it was observed a statistically significant difference between the study groups (p<0.0001), with a lower mean value observed for Active group (0.3; SD=0.3) than in the Placebo group (0.6; SD=0.3).

**Table 11 – Proportion of evacuation with strain – Treatment period – ITT Population**

| Proportion of evacuation with strain | Treatment period | |
|---|---|---|
| | Placebo N=41 | Active N=43 |
| Mean (S.D) | 0.6 (0.3) | 0.3 (0.3) |
| Median | 0.6 | 0.2 |
| Min-Max | 0.0 - 1.0 | 0.0 - 1.0 |
| p-value | <0.0001 | |

- Proportion of evacuation with incomplete sensation.

About the proportion of feeling of incomplete evacuation (Table 12), it was observed a statistically significant difference between the study groups (p=0.0009), with a lower mean value observed for Active group (0.3; SD=0.3) than in the Placebo group (0.6; SD=0.3).

**Table 12– Proportion of evacuation incomplete sensation – Treatment period - ITT Population**

| Proportion of evacuation with incomplete sensation | Treatment period | |
|---|---|---|
| | Placebo N=41 | Active N=43 |
| Mean (S.D) | 0.6 (0.3) | 0.3 (0.3) |
| Median | 0.5 | 0.3 |
| Min-Max | 0.0 - 1.0 | 0.0 - 1.0 |
| p-value | 0.0009 | |

**Efficacy results (continuation):**

- Proportion of blocked stools.

About the proportion of blockage sensation (Table 13), it was observed a statistically significant difference between the study groups (p=0.0001), with a lower mean value observed for Active group (0.2; SD=0.3) than in the Placebo group (0.5; SD=0.4).

**Table 13– Proportion of blocked stools – Treatment period - ITT Population**

| Proportion of blocked stools | Treatment period | |
|---|---|---|
| | Placebo N=41 | Active N=43 |
| Mean (S.D) | 0.5 (0.4) | 0.2 (0.3) |
| Median | 0.4 | 0.1 |
| Min-Max | 0.0 - 1.0 | 0.0 - 1.0 |
| p-value | 0.0001 | |

- Proportion of manual maneuvers to facilitate defecation.

It was observed a statistically significant difference (p=0.024) between Placebo and Active groups about the proportion of manual maneuvers to facilitate defecation: mean and SD of 0.3 (SD=0.4) for Placebo and mean of 0.1 (SD=0.3) for Active Group (Table 14).

**Table 14– Proportion of manual maneuvers to facilitate defecation – Treatment period - ITT Population**

| Proportion of manual maneuvers | Treatment period | |
|---|---|---|
| | Placebo N=41 | Active N=43 |
| Mean (S.D) | 0.3 (0.4) | 0.1 (0.3) |
| Median | 0.0 | 0.0 |
| Min-Max | 0.0 - 1.0 | 0.0 - 1.0 |
| p-value | 0.024 | |

- Adherence to the recommendations about the need of a diet rich in fibers, suitable water intake and physical exercise for CFC improvement.

Concerning the number of days that the patients had adopted the recommendations about diet and physical exercise, according to the information provided diary, there was no significant difference (p=0.126) between the study groups Active and Placebo in the Treatment period , even in the Active group the adherence observed is lower than in the placebo group (Table 15).

About the proportion of patients who adhered to the recommendations at least in a half of the treatment period duration, 80.5% of the patients in the Placebo group and 74.4% in the Active had adopted the recommendations (Table 16).

**Efficacy results (continuation):**

**Table 15– Number of days of adherence to the diet and physical exercise – Treatment period - ITT Population**

| Adherence to the reccomendations about diet and physical exercise * | Treatment period | |
|---|---|---|
| | Placebo N=41 | Active N=43 |
| Mean (S.D) | 13.1 (11.8) | 9.4 (10.6) |
| Median | 11 | 6 |
| Min-Max | 0 - 30 | 0 - 30 |
| p-value | 0.126 | |

* Number of days according to the patient diary

**Table 16– Proportion of patients who adhered to the diet and physical exercise – Treatment period - ITT Population**

| Adherence to the reccomendations about diet and physical exercise* | Treatment period | |
|---|---|---|
| | Placebo N=41 | Active N=43 |
| Adherence | 39 (95.1%) | 42 (97.7%) |
| entire period | 7 (17.1%) | 5 (11.6%) |
| more tha a half of days | 26 (63.4%) | 27 (62.8%) |
| less than a half of days | 6 (14.6%) | 10 (23.3%) |
| Non adherence | 2 (4.9%) | 1 (2.3%) |

- Rescue medication usage.

Concerning the usage of rescue medication during the treatment period, it was observed a statistically significant difference between study groups for proportion of patients who had used (p=0.029) and the number of days of usage (p=0.006). For Placebo group the usage of rescue medication was greater than in the Active group (Table 17) for both perspectives.

**Table 17 – Rescue medication usage – Treatment period - ITT Population**

| Rescue medication | Treatment period | | p-value |
|---|---|---|---|
| | Placebo N=41 | Active N=43 | |
| Proportion of patients who had used | 26 (63.4%) | 17 (39.5%) | 0.029 |
| Number of days of usage | | | |
| Mean (S.D) | 5.3 (6.0) | 2.0 (4.4) | |
| Median | 3 | 0 | 0.006 |
| Min-Max | 0 - 19 | 0 - 20 | |

**Efficacy results (continuation):**

- Level of constipation improvement, according to the patient evaluation.

At the end of treatment period, the evaluation about the improvement of the constipation was classified as better or much better: 70.7% of the patients in the Placebo group and 95.3% of the patients in the Active group. It was observed a statistically significant difference between them (p=0.0015) (Table 18).

**Table 18 – Constipation improvement according to the patient evaluation – Treatment period - ITT Population**

| Constipation improvement - patient evaluation | Treatment period | |
|---|---|---|
| | Placebo N=41 | Active N=43 |
| Much better | 10 (24.4%) | 24 (55.8%) |
| Better | 19 (46.3%) | 17 (39.5%) |
| Unchanged | 12 (29.3%) | 2 (4.7%) |
| Worse | 0 | 0 |
| Much worse | 0 | 0 |
| p-value | 0.0015 | |

- Logistic Regression model for GIC.

The results indicated that the overall model was statistically significant (p<.0001), however the variable *number of days with adherence to the recommendations about diet and physical exercises* were not statistically significant (Wald Chi-square = 0.8104, p = 0.3680) as a predictor of GIC. The other two variables considered in the model were statistically significant: *number of days of rescue medication usage* (Wald Chi-square = 4.6308, p = 0.0314) and *Treatment Group* (Wald Chi-square = 9.0240, p = 0.0027).

As a second step, a new model was adjusted excluding the variable not statistically significant in the first model. The overall model was statistically significant (p<0.0001). The variables *number of days of rescue medication usage* (Wald Chi-square = 5.9382; p = 0.0148) and *Treatment Group* (Wald Chi-square = 9.4576; p = 0.0021) were found to be significant in predicting the occurrence of GIC. The regression coefficients estimated throw the model adjusted were 0.844 ($CI_{95\%}$: [0.736; 0.967]) for *number of days of rescue medication usage* and 4.990 ($CI_{95\%}$: [1.791; 13.900]) for *Treatment Group*. Interpreting these coefficients in terms of odds ratio:

- Increasing one day in the *use of rescue medication* it would be expected about 16% of reduction in chance of GIC;
- It is expected about 400% of increasing in the chance of GIC for the Active Group in relation to the Placebo Group;

**Safety results:**

From the 48 patients randomized to the Active group, 39 (81.3%) patients had reported some adverse event during the study period (pre-inclusion, treatment and follow up phases), totalizing 259 events. From the 48 patients randomized to the placebo group, 41 (85.4%) patients had reported some adverse event in the study period, totalizing 335 events (Table 19).

**Table 19: Summary of the number of adverse events reported by the ITT Population, per study period.**

| | Placebo | | Active | |
|---|---|---|---|---|
| | n / N | % | n / N | % |
| Patients with AE | | | | |
| Pre-inclusion | 34/48 | 70.8% | 30/48 | 62.5% |
| Treatment | 35/48 | 72.9% | 33/46 | 68.8% |
| Follow up | 19/38 | 50.0% | 14/40 | 35.0% |
| Any period | 41 | 85.4% | 39 | 81.3% |
| Number of AEs reported | | | | |
| Pre-inclusion | 78/335 | 23.3% | 80/259 | 30.9% |
| Treatment | 159/335 | 47.5% | 136/259 | 52.5% |
| Follow up | 98/335 | 29.2% | 43/259 | 16.6% |
| Any period | 335 | 100% | 259 | 100% |

All the events were considered as recovered, and no serious adverse events were reported. There was only one case of pregnancy, in which the patient was discontinued of the study and then followed up by the investigator. The patient had normal birth, in University Hospital of ULBRA (Canoas – Rio Grande do Sul). Until the last contact by phone (on August 2nd 2012), the child was healthy and with normal development.

In the placebo group, 32.6% (15/46) of the patients reported at least one adverse event considered as related to the medication, in the treatment phase. In the Active group, this percentage was 50.0% (23/46) (Table 20).

In both groups, the most frequent adverse events reported in the treatment phase were headache, meteorism and abdominal pain. The percentages of patients who presented them were, respectively: 35.4%, 31.2% and 27.1% in the placebo group; 33.3%, 22.9% and 27.1% in the Active group.

**Table 20: Summary of Adverse events reported**

| Adverse event | Placebo | | Active | |
|---|---|---|---|---|
| | # patients (%) N = 48 | # reports (%) N = 159 | # patients (%) N = 48 | # reports (%) N = 136 |
| Any | 35 (72.9%) | 159 (100%) | 33 (68.8%) | 136 (100%) |
| Related to study medication | 15 (31.3%) | 41 (25.8%) | 23 (47.9%) | 57 (41.9%) |
| Serious | 0 | 0 | 0 | 0 |
| Serious and related to study medication | 0 | 0 | 0 | 0 |
| Causing death | 0 | 0 | 0 | 0 |
| Related to study medication and causing death | 0 | 0 | 0 | 0 |
| Leading to treatment withdrawal* | 2 (4.2%) | 7 (14.6%) | 0 | 0 |
| Related to study medication and leading to treatment withdrawal* | 2 (4.2%) | 7 (14.6%) | 0 | 0 |

* The two patients who had AEs related to study medication and leading to treatment withdrawal were:

- stomach pain, nausea and reflux.
- abdominal pain, abdominal edema, meteorism and vomiting.

| | |
|---|---|
| **Date of issue:** | 18 October 2012 |