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Sponsor / Company: Sanofi	**Study Identifiers:** NCT00994851
Drug substance(s): Senna + Cassia	**Study code:** SENCA_L_04746

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:

Date first patient enrolled: 22-Sep-2009

Date last patient completed: 03-Aug-2012

Phase of development: III

Objectives:

Primary endpoint:

- To evaluate the clinical efficacy of the composition Cassia Fistula+ Senna Alexandrina Miller (capsule) during a treatment period of 30 days, in patients with Chronic Functional Constipation (CFC), considering the following criteria:

- Frequency of evacuation during the treatment and follow-up period;

- Consistency of stools during the treatment and follow-up period according to the Bristol Scale;

- Global improvement of 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);

Secondary endpoints:

- Number of days without evacuation;

- Proportion of evacuation with: pain, strain, incomplete sensation, blocked stools and usage of manual maneuvers to facilitate the defecation;

- Proportion of patients who adhere to the recommendations about the diet rich in fibers, suitable Water Intake and physical exercise;

- Proportion of patients who had used the rescue medication;

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

- Adverse events occurrence.

Methodology:

Unicentric, randomized (1:1), double blind, parallel, placebo controlled study comprising three periods as below:

Screening Period

V0: Screening visit;

- Diagnosis of CFC (according to the ROME III criteria)
- Delivery of Instructions about the need of a diet rich in fibers, suitable water Intake and physical exercise for CFC improvement.

Pre-treatment Period (10 days)

V1: Randomization visit (D0);

- 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.
- Randomization

Treatment Period (30 days)

V2: After 15 days of treatment;

V3: After 30 days of treatment; (end of treatment)

Follow-up Period (30 days)

V4: About 30 days after treatment completion

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.

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 period, the study medication (active or placebo) should not be interrupted.

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.

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 (48 per treatment arm)
	Randomized:	96 (48 per treatment arm)
	Treated:	96
Evaluated:	Efficacy:	86
	Safety:	96
	Pharmacokinetics:	NA

Diagnosis and criteria for inclusion:

- Diagnosis of Chronic Functional Constipation according to the ROME IIII criteria;
- Majority of the stool classified as type 1 or 2 according to the Bristol Stool Scale;
- age ≥ 18 and ≤ 59 years old;
- No previous history or current neurological and/or metabolic disorder and/or endocrine disorder;
- No constipation caused by previous surgery;
- No intestinal obstruction including colon/rectum cancer ;
- No Irritable bowel syndrome or inflammatory bowel disease;
- No continuous treatment with the following: analgesics, anticholinergic (antihistamines, antispasmodics, antidepressants, antipsychotics) iron supplements or aluminium, opiates, antihypertensive, calcium channel blockers and ganglion blocker;

Study treatments

Investigational medicinal product(s):

Formulation: Naturetti® (Cassia Fistula + Senna Alexandrina Miller) capsules. (box contained 30 capsules)

Route(s) of administration: Oral

Dose regimen: Daily administration of one capsule at bedtime, during 30 days.

Noninvestigational medicinal product(s)

Formulation: Placebo of Naturetti® (Cassia Fistula + Senna Alexandrina Miller). (box contained 30 capsules)

Route(s) of administration: Oral

Dose regimen: Daily administration of one capsule at bedtime, during 30 days.

Duration of treatment: 30 days

Duration of observation: 70 days. About 10 days (pre-treatment period) + 30 days (treatment period) + 30 days (follow-up period)

Criteria for evaluation:

Efficacy:

Primary:

- 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);

- 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;

- 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.

Secondary:

- 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.

- Proportion of evacuation with pain;

- Proportion of evacuation with strain;

- Proportion of evacuation with incomplete sensation;

- Proportion of blocked stools;

- Proportion of manual maneuvers to facilitate defecation;

- Proportion of subjects who adhere to the diet recommendation;

- Proportion of the patients who had used rescue medication;

- Level of constipation improvement, according to the patient evaluation: 1 - Much better, 2 - Better, 3 - Unchanged; 4 – Worse; 5 – Much Worse.

Safety:

Adverse events reported by the patient or noted by the investigator.

Pharmacokinetics: NA

Statistical methods:

Sample Size rational

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%.

Methodology

All randomized patients who had used at least one dose of the study drugs were considered in the Intent-to-treat (ITT) population. The population consisted of all patients who were randomized, received at least one dose of investigational product (IP) and had at least one assessment of any primary or secondary efficacy variables, irrespective of compliance with the study protocol and procedures were considered in the Modified Intent to Treat (m-ITT) population. From this total, the patients who completed all study periods, without any major protocol violations were considered in the Per-Protocol (PP) population. Major protocol violations were defined independently of the identification of the treatment.

The safety analyses were conducted based on the ITT population. The efficacy analyses were conducted based on the mITT population. The analyses concerning the primary objective were also performed based on the PP Population and ITT population as an analysis of sensitivity

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.

All tests applied were performed using Statistical Package for the Social Sciences (SPSS) (version 15.0). It was adopted a statistical significance level of 5%.

Primary analysis

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.

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:

- An increasing in the MEF in the treatment period in comparison to the pre-treatment;

- A 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 GIC it was also calculated the Confidence Interval $CI_{95\%}$ for the difference between GIC in the Active Group and in the Placebo Group.

Secondary analysis

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.

A Logistic Regression model using SAS version 9.1 for mITT 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:

- Response variable
    - GIC (Yes or No);
- Predictor variables
    - Number of days of rescue medication usage;
    - Number of days with adherence to the recommendations about diet and physical exercises.
    - Treatment Group: Placebo and Active.

Summary:

Population characteristics:

Introduction

This trial was initially a phase IV, non-comparative study, with two periods lasting 30 days. In the first period the patient should not receive any treatment (the patient should only intake the rescue medication when necessary) and in the 2nd period the patient should receive Naturetti.

After EC approval, the study was submitted to ANVISA and the patient recruitment was started according to the local regulation for a local phase IV study.

However, after the inclusion of 12 patients, the Sanofi received from ANVISA a request about the modification of the study to a phase III, with a comparative design with placebo. At that moment, all 12 patients included in the study were in the first period and they were withdrawal from the study without any intake of medication. The FPI and LPO of these patients were respectively 22-Sep-2009 and 14-Oct-2009.

Patients enrollment

After the ANVISA requesting about the modification of the study to a comparative design with placebo: Between 08-Sep-2010 and 18-May-2012, 136 patients were enrolled to the study. From this total, 40 (29,4%) patients 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.

Demographic data

The age of patients at time of inclusion ranged from 18 to 59 years, with a mean age of 40,1 (SD=12,4) years for Placebo Group and from 20 to 59 years, with a mean age of 43.5 (SD=10.1) years for Active Group. The median age in the Placebo group was 40 years and for Active group, 45 years. There was no statistically significant difference between groups regarding age (p-value=0.147).

About patients' ethnicity, most of patients were Caucasian: 39 (81,3%) and 44 (91.7%) patients, respectively, in the Placebo and Active Groups. In the Placebo Group 8 (16,7%) patients were black and 1 (2,1%) were multi-racial. The other 4 (8,3%) patients in Active Group were black.

The most of the patients randomized were women: in the placebo group 46 (95.8%) patients and in the Active group all of them were women.

Study Populations

136 patients screened

↓ 40 patients: Screening Failure

96 patients randomized (48 per Group) - **ITT Population**[1]

V2 not performed:

3 Placebo: 1 Consent withdrawal / 2 Lost to follow up

3 Active: 1 Consent withdrawal / 1 Lost to follow up / 1 disease in the family

↓

V3 not performed:

2 Placebo: 1 Non-adherence to the study treatment [2] / 1 Consent withdrawal

2 Active: 1 Non-adherence to the study treatment [2] / 1 Lost to follow up

86 patients (43 Placebo; 43 Active) - **mITT Population**

↓ 4 Placebo: 3 Lost to follow up / 1 Consent withdrawal

↓ 2 Active: 1 Consent withdrawal / 1 Lost to follow up

80 patients (39 Placebo; 41 Active) - **PP Population**

[1] Patients received at least one dose of study medication

[2] The patient received less than 80% of the planned study medication

Study Period

From the 96 patients enrolled to the study, 86 (89.6%) 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 Group N=48	Active Group N=48	Total N=96
V1 Randomization visit	48 (100.0%)	48 (100.0%)	96 (100.0%)
V2 (15 days) Treatment period	45 (93.8%)	45 (93.8%)	90 (93.8%)
V3 (30 days) Treatment period	43 (89.6%)	43 (89.6%)	86 (89.6%)
V4 (60 days) Follow up period	39 (81.3%)	41 (85.4%)	80 (83.3%)

Number of days of study medication intake – ITT population.

Comparing the number of days with study medication intake between study groups (Table 2) there was not found a statistically significant difference between them (p-value=0.8390).

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

Number of days	Treatment period	
	Placebo * N=48	Active * N=48
Mean (S.D)	28.6 (4.4)	28.4 (3.8)
Median	30	29
Min-Max	5 - 30	9 - 30
p-value	0.8390	

* For three patients of each group the information is missing due to they did not attend the visit V2

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 the Placebo group three patients had used non-allowed medications during the treatment period: ibuprofen (1 and 2 days) and complex of multi vitamins and minerals* (4 days). In the Active group, none patients had used non-allowed medications during treatment period.

* A, B1, B2, B5, B6, B12, C, D, Iron, lysine, niacin, magnesium, manganese, threonine and zinc.

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: 0.45 (SD=0.30) for Placebo group and 0.39 (SD=0.24) for Active group. It was not detected difference between them (p=0.253) (Table 3).

In the treatment period, it was observed a statistically significant difference between the groups (p=0.003). The mean number of evacuation were higher in the Active group 0.92 (SD=0.38) than in the placebo one 0.68 (SD=0.35) (Table 3).

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

MEF	Pre-treatment period		Treatment period	
	Placebo N=43	Active N=43	Placebo N=43	Active N=43
Mean (S.D)	0.45 (0.30)	0.39 (0.24)	0.68 (0.35)	0.92 (0.38)
Median	0.4	0.3	0.6	0.8
Min-Max	0.0 - 1.6	0.0 - 1.2	0.2 - 1.8	0.3 - 1.8
p-value	0.253		0.003	

- 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: 0.20 (SD=0.30) for Placebo group and 0.20 (SD=0.20) for Active group. It was not detected statistical significant difference between them (p=0.621) (Table 4).

In the treatment period, it was observed a statistically significant difference between the groups (p=0.0002). The mean number of evacuation classified as type>2 were higher in the Active group 0.64 (SD=0.33) than in the placebo 0.36 (SD=0.33) group (Table 4).

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

MCS	Pre-treatment period		Treatment period	
	Placebo N=43	Active N=43	Placebo N=43	Active N=43
Mean (S.D)	0.20 (0.30)	0.20 (0.30)	0.36 (0.33)	0.64 (0.33)
Median	0.0	0.0	0.3	0.7
Min-Max	0.0 - 1,0	0.0 - 1.0	0.0 - 1.0	0.0 - 1.0
p-value	0,621		0,0002	

- Global Improvement of Constipation (GIC) – mITT Population

For the mITT 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 95% of the patients in the Active group and 72% 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=0.0035), leading to a Relative Risk (Active/Placebo) of 1.3226 and a respective $CI_{95\%}$ of [1.0857; 1.6111] (Table 5).

For MCS, in the Active group, about 65 % of the patients, and in the Placebo group, about 26% of the patients, had evacuations predominantly classified as type>2 in the treatment period (p=0.0002), leading to a Relative Risk (Active/Placebo) of 2.5455 and a respective $CI_{95\%}$ of [1.4616; 4.4329] (Table 5).

The proportion of patients who presented GIC was 62.8% in the Active group and 23.3% in the Placebo group (p=0.0002). 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 [20.3%; 58.7%] (Table 5).

The Relative Risk indicated an increasing in the GIC for Active group in relation to the Placebo of 2.7000, with an associated $CI_{95\%}$ of [1.4971; 4.8693] (Table 5).

Table 5 – Primary Efficacy parameters – mITT Population

mITT	Placebo (N=43)	Active (N=43)	χ^2; p-value	RR (Active/Placebo); $CI_{95\%}$
MEF	31 (72.1%)	41 (95.4%)	8.5317; p=0.0035	1.3226; [1.0857; 1.6111]
MCS	11 (25.6%)	28 (65.1%)	13.5592; p=0.0002	2.5455; [1.4616; 4.4329]
GIC	10 (23.3%)	27 (62.8%)	13.7088; p=0.0002	2.7000; [1.4971; 4.8693]
Difference between Groups (GIC): 62.8% - 23.3% = 39.5% - CI95%: [20.3%; 58.7%]				

- Global Improvement of Constipation (GIC) – ITT Population

The results found in the ITT population were very similar to those observed in the mITT population. With this sensitivity analyses it was observes that in the most conservative approach it is still possible to observe a statistical significant difference between study groups (Table 5a).

Table 5a – Primary Efficacy parameters – ITT Population

ITT	Placebo (N=48)	Active (N=48)	χ^2; p-value	RR (Active/Placebo); $CI_{95\%}$
MEF	31 (64.6%)	41 (85.4%)	5.5556; p=0.0184	1.3226; [1.0405; 1.6812]
MCS	11 (22.9%)	28 (58.3%)	12.4804; p=0.0004	2.5455; [1.4377; 4.5068]
GIC	10 (20.8%)	27 (56.3%)	12.7091; p=0.0004	2.7000; [1.4740 ; 4.9458]
Difference between Groups (GIC): 56.3% - 20.8% = 35.5% - CI95%: [17.3%; 53.6%]				

- Global Improvement of Constipation (GIC) – PP Population

The results found in the PP population were very similar to those observed in the mITT 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 40.2% with an associated $CI_{95\%}$ of [20.3%; 60.2%]. The Relative Risk indicated an increasing in the GIC for Active group in relation to the Placebo of 2.5683, with an associated $CI_{95\%}$ of [1.4407; 4.5785] (Table 6).

Table 6 – Primary Efficacy parameters – PP Population

PP	Placebo (N=39)	Active (N=41)	χ^2; p-value	RR (Active/Placebo); $CI_{95\%}$
MEF	29 (74.4%)	39 (95.1%)	6.7581; p=0.0093	1.2792; [1.0506; 1.5576]
MCS	11 (28.2%)	28 (68.3%)	12.8561; p=0.0003	2.4213; [1.4076; 4.1650]
GIC	10 (25.6%)	27 (65.9%)	13.0015; p=0.0003	2.5683; [1.4407; 4.5785]
Difference between Groups (GIC): 65.9% - 25.6% = 40,2% - CI95%: [20.3%;60.2%]				

- 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<0.0001). The mean of evacuation frequency was greater in the treatment period (0.92; SD=0.38) than in the follow-up period (0.58; SD=0.24). For the Placebo group there was no found a statistically significant difference (p=0.765) between the two study periods (Table 7) for MEF

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

MEF	Placebo Group (N=43)		Active Group (N=43)	
	Treatment period	Follow-up period	Treatment period	Follow-up period
Mean (S.D)	0.68 (0.35)	0.71 (0.34)	0.92 (0.38)	0.58 (0.24)
Median	0.6	0.7	0.8	0.5
Min-Max	0.2 - 1.8	0.1 - 1.6	0.3 - 1.8	0.3 - 1.1
p-value	0.765		<0.0001	

- 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<0.0001). The mean number of evacuations classified according to the Bristol Scale as type>2 was greater in the treatment period (0.64; SD=0.33) than in the follow-up period (0.48; SD=0.36). For the Placebo group there was not found a statistically significant difference (p=0.945) between the two study periods for MCS (Table 8).

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

MCS	Placebo Group (N=43)		Active Group (N=43)	
	Treatment period	Follow-up period	Treatment period	Follow-up period
Mean (S.D)	0.36 (0.33)	0.36 (0.37)	0.64 (0.33)	0.48 (0.36)
Median	0.3	0.3	0.7	0.4
Min-Max	0.0 - 1.0	0.0 - 1.0	0.0 - 1.0	0.0 - 1.0
p-value	0.945		<0.0001	

Secondary endpoints

- Number of days without evacuation

About the mean days without evacuation (Table 9) it was observed a statistically significant difference (p=0.0129) between Placebo and Active groups, respectively with mean and SD of 3.4 (SD=2.1) and 2.4 (SD=1.2).

Table 9 – Number of days without evacuation – Treatment period – mITT Population

Number of days without evacuation	Treatment period	
	Placebo N=43	Active N=43
Mean (S.D)	3.4 (2.1)	2.4 (1.2)
Median	3	2.0
Min-Max	0 - 11	1 - 5
p-value	0.0129	

- Proportion of evacuation with pain

About the proportion of evacuation with pain (Table 10) in the treatment period, it was observed a statistically significant difference (p=0.0176) between groups. In the Placebo group the mean (0.30; SD=0.30) was greater than in the Active group (0.16; SD=0.21).

Table 10 – Proportion of evacuation with pain – Treatment period – mITT Population

Proportion of evacuation with pain	Treatment period	
	Placebo N=43	Active N=43
Mean (S.D)	0.30 (0.30)	0.16 (0.21)
Median	0.20	0.10
Min-Max	0.0 - 1.00	0.0 - 1.0
p-value	0.0176	

- 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-0.0083), with a lower mean value observed for Active group (0.32; SD=0.31) than in the Placebo group (0.52; SD=0.35).

Table 11 – Proportion of evacuation with strain – Treatment period – mITT Population

Proportion of evacuation with strain	Treatment period	
	Placebo N=43	Active N=43
Mean (S.D)	0.52 (0.35)	0.32 (0.31)
Median	0.50	0.20
Min-Max	0.0 - 1.0	0.0 - 1.0
p-value	0.0083	

- 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=0.0030), with a lower mean value observed for Active group (0.32; SD=0.31) than in the Placebo group (0.53; SD=0.33).

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

Proportion of evacuation with incomplete sensation	Treatment period	
	Placebo N=43	Active N=43
Mean (S.D)	0.53 (0.33)	0.32 (0.31)
Median	0.50	0.20
Min-Max	0.0 - 1.0	0.0 - 1.0
p-value	0.0030	

- Proportion of blocked stools

About the proportion of blockage sensation (Table 13), it was observed a statistically significant difference between the study groups (p=0.0048), with a lower mean value observed for Active group (0.20; SD=0.25) than in the Placebo group (0.38; SD=0.33).

Table 13– Proportion of blocked stools – Treatment period - mITT Population

Proportion of blocked stools	Treatment period	
	Placebo N=43	Active N=43
Mean (S.D)	0.38 (0.33)	0.20 (0.25)
Median	0.30	0.1
Min-Max	0.0 - 1.0	0.0 - 1.0
p-value	0.0048	

- Proportion of manual maneuvers to facilitate defecation

It was observed a statistically significant difference (p=0.0487) between Placebo and Active groups about the proportion of manual maneuvers to facilitate defecation: mean and SD of 0.13 (SD=0.27) for Placebo and mean of 0.04 (SD=0.11) for Active Group (Table 14).

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

Proportion of manual maneuvers	Treatment period	
	Placebo N=43	Active N=43
Mean (S.D)	0.13 (0.27)	0.04 (0.11)
Median	0.0	0.0
Min-Max	0.0 - 1.0	0.0 - 0.5
p-value	0.0487	

- 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=0.109) 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, 79.1% of the patients in the Placebo group and 83.7% in the Active had adopted the recommendations (Table 16).

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

Adherence to the reccomendations about diet and physical exercise *	Treatment period	
	Placebo N=43	Active N=43
Mean (S.D)	15.0 (12.4)	10.9 (10.9)
Median	13.0	7.0
Min-Max	0 - 30	0 - 30
p-value	0.109	

* Number of days according to the patient diary

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

Adherence to the reccomendations about diet and physical exercise*	Treatment period	
	Placebo N=43	Naturetti N=43
Adherence	43 (100.0%)	43 (100.0%)
entire period	9 (20.9%)	5 (11.6%)
more tha a half of days	25 (58.1%)	31 (72.1%)
less than a half of days	9 (20.9%)	7 (16.3%)
Non adherence	-	-

- 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=0.0024) and for the number of days of usage (p=0.0202). 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 - mITT Population

Rescue medication	Treatment period		p-value
	Placebo N=43	Naturetti N=43	
Proportion of patients who had used	30 (69.8%)	17 (39.5%)	0.0024
Number of days of usage			
Mean (S.D)	4.6 (6.0)	2.0 (3.7)	
Median	2	0	0.0202
Min-Max	0 - 24	0 - 16	

- 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: 55.8% of the patients in the Placebo group and 93.0% of the patients in the Active group. It was observed a statistically significant difference between them (p=0.0007) (Table 18).

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

Constipation improvement - patient evaluation	Treatment period	
	Placebo N=43	Naturetti N=43
Much better	8 (18.6%)	19 (44.2%)
Better	16 (37.2%)	21(48.8%)
Unchanged	17 (39.5%)	3 (7.0%)
Worse	2 (4.7%)	0
Much worse	0	0
p-value	0.0007	

- 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 = 0.4149, p = 0.5195) 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 = 6.5457,
p = 0.0105) and *Treatment Group* (Wald Chi-square = 9.1678, p = 0.0025).

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 = 6.4219; p = 0.0113) and *Treatment Group* (Wald Chi-square = 8.9190; p = 0.0028) were found to be significant in predicting the occurrence of GIC. The regression coefficients estimated throw the model adjusted were 0.812 ($CI_{95\%}$: [0.681; 0.954]) for *number of days of rescue medication usage* and 4.535 ($CI_{95\%}$: [1.680; 12.185]) 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 19% of reduction in chance of GIC;
- It is expected about 350% of increasing in the chance of GIC for the Active Group in relation to the Placebo Group;

Safety results:

From the 12 patients enrolled to the study before the design modification to a comparative study, there is some Adverse event reported for two patients. The events reported were abdominal pain and intestinal cramps and they were not considered related to the study medication as they occurred during the pre-treatment phase.

From the 48 patients randomized to the Active group, 42 (87.5%) patients had reported some adverse event during the study period (pre-treatment, treatment and follow up periods), totalizing 306 events. From the 48 patients randomized to the placebo group, 39 (81.3%) patients had reported some adverse event in the study period, totalizing 284 events (Table 19).

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

	Placebo Group		Active Group	
	n / N	%	n / N	%
Patients with AE				
Pre-inclusion	37/48	77.1%	35/48	72.9%
Treatment	35/48	72.9%	34/48	70.8%
Follow up	19/39	48.7%	21/41	51.2%
Any period	39	81.3%	42	87.5%
Number of AEs reported				
Pre-inclusion	109 / 284	38.4%	89 / 306	29.1%
Treatment	121 / 284	42.6%	155 / 306	50.7%
Follow up	54 / 284	19.0%	62 / 306	20.3%
Any period	284	100%	306	100%

All the events were considered as recovered, and no serious adverse events was reported.

In the placebo group, 16.7% (8/48) of the patients reported at least one adverse event considered as related to the medication, during treatment period. In the Active group, this percentage was 41.7% (20/48) (Table 20).

The most frequent adverse events reported in the treatment phase, for both groups, were showed in the Table 21. Meteorism, abdominal pain, headache and intestinal cramps were the most common AEs reported in the active group. For Placebo group, the most common AES reported were meteorism and headache.

Table 20: Summary of Adverse events reported – Treatment period – ITT population

Adverse events - Treatment Period	Placebo Group		Active Group	
	# patients (%)	# reports (%)	# patients (%)	# reports (%)
	N = 48	N = 121	N = 48	N = 155
Any	35 (72.9%)	121 (100%)	34 (70.8%)	155 (100%)
Related to study medication	08 (16.7%)	18 (14.9%)	20 (41.7%)	48 (31.0%)
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	0	0	0	0
Related to study medication and leading to treatment withdrawal	0	0	0	0

Table 21: Summary of Adverse events more frequent – Treatment period – ITT population

Adverse events Treatment Period	Placebo Group (N=48)		Active Group (N=48)	
	n	%	n	%
Meteorism	14	29.2	11	22.9
Abdominal pain	3	6.3	13	27.1
Headache	20	41.7	11	22.9
Intestinal cramps	4	8.3	10	20.8
Diarrhea	3	6.3	4	8.3
Nausea	1	2.1	9	18.8

Pharmacokinetic results: NA

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