

## **TITLE PAGE**

### **Title:**

**Xyloglucan for the treatment of acute gastroenteritis in children: results of a randomized, controlled, open-label, parallel group, multicentre, national clinical trial**

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## **ABSTRACT**

**Specific objective:** To assess the efficacy, safety and time of onset of the antidiarrheal effect of xyloglucan (Xilaplus<sup>®</sup>, containing xyloglucan) in children with acute gastroenteritis receiving oral rehydration solution (ORS).

**Methods:** This randomized, controlled, open-label, parallel group, multicentre, clinical trial included children (from 3 months to 12 years old) with acute gastroenteritis of infectious origin.

Children were randomized to receive a 5-day treatment. Both control and active groups received ORS and active group also received xyloglucan (Xilaplus<sup>®</sup>, one sachets/8 hours in children younger than 3 years and 2 sachets/8 hours in children between 3 and 12 years). Diarrheal symptoms and safety were assessed in 3 visits (baseline, at 2 and 5 days) and by phone call at 10 days, and by fulfillment of a diary card by the parents or legal representatives.

The number and characteristics of stools (type 6 and 7 on Bristol Scale) and the evolution of other diarrheal symptoms (nausea, vomiting, abdominal pain, flatulence, fever and dehydration) were assessed during the 72 hours previous to baseline and, after inclusion, at 24-hour intervals (during the first day of treatment assessments were performed at 1, 3, 6, 12 and 24 hours). Occurrence of adverse events was recorded during the whole study period.

**Results:** A total of 36 patients (58.33% girls; age: 13.88% ≤ 1 year, 47.22% 1-5 years, 25.00% 5-10 years, 13.88% >10 years) were included (n = 18 in each group). The group treated with xyloglucan and ORS had a better evolution of symptoms than the group receiving ORS alone. A faster onset of action was observed in the xyloglucan group compared with the control group, since at 6 hours, xyloglucan produced a statistically significant higher decrease in the number of type 7 stools (0.11 vs 0.44; p=0.027). At days 3 and 5, xyloglucan was also able to produce a statistically significant higher reduction of type 6 and 7 stools in comparison with ORS alone (p=0.026 and 0.034, respectively). A better evolution of nausea, vomiting and abdominal pain was also recorded for the xyloglucan group, although the differences vs the control group were not statistically significant. Xyloglucan plus ORS was safe and well tolerated, without the occurrence of adverse events throughout the study.

**Conclusions:** Xyloglucan is a fast, efficacious and safe option for the treatment of acute gastroenteritis in children, with a rapid onset of action in reducing diarrheal symptoms.

**KEY WORDS:** acute gastroenteritis, diarrhea, efficacy, safety, onset of action, xyloglucan, mucosal protectors, stools, children.

## BACKGROUND

Acute gastroenteritis, characterized by the onset of diarrhea with or without vomiting, is an extremely common problem in childhood, and the second leading cause of morbidity and mortality worldwide, particularly in the first 3 years of life (Guarino et al, 2008; Ciccarelli et al, 2013), with the majority of deaths concentrated in 35 'low income' countries (O'Ryan et al, 2014).

In Europe, it is usually, although not always, a mild disease, and death is an exceptional outcome. However, gastroenteritis is associated with a substantial number of hospitalisations and high costs (Guarino et al, 2008).

The severity of gastroenteritis is related to aetiology rather than to age, and rotavirus is responsible for the most severe cases, being microbiological investigations generally not needed (Guarino et al, 2008).

According to the Guidelines for age management in European children, rehydration is the key treatment and should be applied as soon as possible. Reduced osmolality oral rehydration solution should be used, and it should be offered ad libitum and rapidly (i.e., within 3–4 hours). Regular feeding should not be interrupted and should be carried on following initial rehydration. Drugs are generally not necessary; however, selected probiotics may reduce the duration and intensity of symptoms. Antibiotic therapy is not needed in most cases of acute gastroenteritis and may induce a carrier status in case of *Salmonella* infection. Antibiotic treatment is effective mainly in shigellosis and in the early stage of *Campylobacter* infection. According to these guidelines, other drugs may be effective but require further investigations (Guarino et al, 2008).

In this scenario, there is a need to develop new products that could be used in combination with oral rehydration solutions (ORS) to reduce the duration and the number of symptoms, with a good safety profile (Dickinson and Surawicz, 2014; Vandenplas et al, 2013). Food supplements and medical devices can provide these requirements, although randomized, controlled studies are still needed (Vandenplas et al, 2013).

Currently, a new class of products has been developed and currently used in gastroenteric diseases, which may be defined as “mucosal protectors”, which form a bio-protective film on the intestinal mucosa, improving the resistance of the mucosa to pathologic aggressions, helping to restore the

normal function (Ruszczyński et al, 2014; Franceschi et al, 2014). Among these film-forming products, gelatin tannate, gelatin or xyloglucan are currently being studied and used for gastroenteric disorders, although further randomized studies are needed to completely assess the efficacy of these products in acute diarrhea or acute gastroenteritis in different types of patients (Franceschi et al, 2014; Ruszczyński et al, 2014).

In this regard, a medical device containing xyloglucan, extracted from the seeds of the tamarind tree (*Tamarindus indica*), has developed and has recently received European approval as MED class III for restoring the physiological functions of the intestinal walls (Xilaplus<sup>®</sup>; Novintethical Pharma, SA). In the form of capsules for adults and powder for paediatric use, Xilaplus<sup>®</sup> has been specifically formulated for the control and reduction of symptoms related to diarrheal events of different aetiologies, as abdominal tension and frequent emissions of faeces.

Xyloglucan, if ingested in due amounts, is able to stratify on the intestinal mucosa to form a protective biofilm that improves the resistance of the mucosa to pathologic aggressions and helps to restore its normal function. In particular, xyloglucan has been shown to increase the Trans Epithelial Electrical Resistance (TEER), an index of good function of the mucosal tight junctions, in Caco 2 monolayers, confirming its ability to counteract mucosal permeability and leakage typical of diarrhea. In the same *in vitro* model, xyloglucan has been able to restore normal TEER values after leakage induced with exposure to *E. coli* (Bueno et al, 2014; Sekkal et al, 2015; manuscript in preparation). The same properties of xyloglucan have also been demonstrated *in vivo* by restoring the huge mucosal leakage induced by intra-peritoneal injection of *E. coli* lipopolysaccharide (LPS - 1 mg/kg) in adult rats (Bueno et al, 2014; Sekkal et al, 2015; manuscript in preparation).

In a previous randomized, multicenter, open-label study, we have demonstrated the efficacy and safety of xyloglucan in adult patients with acute diarrhea. In comparison with two widely used anti-diarrheal products, *S. bouliardii*, containing the yeast probiotic *Saccharomyces bouliardii*, and diosmectite, an absorbent activated natural aluminosilicate clay, xyloglucan (Xilaplus<sup>®</sup>) exhibited a faster onset of action in terms of reduction for the mean number of type 6 and 7 stools (the most dehydrating type of stools), particularly during the first hours post-treatment. Xyloglucan was also the most efficient treatment in reducing the percentage of patients with nausea and abdominal pain throughout the study period, with an excellent safety profile (Gnessi et al, 2015-submitted; Gnessi et al, 2015 UEG week congress).

Based on these favourable results in adults, and considering the need to develop new products for the management of acute gastroenteritis in children (Dickinson and Surawicz, 2014; Vandenplas et al, 2013; Guarino et al, 2008), we designed the present randomized, controlled, open-label, parallel group, multicentre, clinical trial to assess the efficacy and safety of xyloglucan (Xilaplus<sup>®</sup> sachets) plus ORS, in comparison ORS alone in pediatric patients (from 3 months to 12 years old) with acute gastroenteritis.

Results obtained have demonstrated that xyloglucan can be an efficacious and safe option to be administrated in combination with ORS to reduce diarrheal symptoms during the first hours.

## **METHODS**

This randomized, controlled, open-label, parallel group, multicentre, clinical trial was performed to evaluate the efficacy and safety of xyloglucan (Xilaplus<sup>®</sup> sachets, containing xyloglucan and gelatin of animal origin) plus ORS, in comparison ORS alone in pediatric patients (from 3 months to 12 years old) with acute gastroenteritis.

The study protocol was approved by the Decision of the Ethical Commission for Scientific Research of the “Targu Mures” University of Medicine and Pharmacy with the no. 60 dated 8 July 2012 and procedures were in accordance with the ethical standards laid down in the Declaration of Helsinki, as revised in the year 2000. Written informed consent was obtained for all children, from the children’s parents or legal guardians in all cases and also from the assent of children aged 7 – 12 years. Patients were recruited in different Romanian outpatient medical offices of general practitioners in the context of their routine clinical practice.

Children with an age range between 3 months and of 12 years and diagnosis of acute gastroenteritis (acute diarrhea) of infectious origin with absent or mild-moderate dehydration that could be treated with ORS and diet (without requiring antibiotic therapy) in an out-patient setting were included in the study. Acute diarrhea was defined as the occurrence of  $\geq 3$  stools per day graded as 6 or 7 on the Bristol Scale scale (Heaton and O’Donnell, 1994; Palsson et al, 2014) during a period shorter than 72 hours. The diagnosis was made according to the investigators’ judgment based on the clinical picture including objective (stools, vomiting and fever) and subjective symptoms (nausea, abdominal pain and bloating).

Potential participants were excluded in case of infantile colic, diarrhea due to milk/protein intolerance, severe dehydration requiring intravenous rehydration, need of hospitalization, use of antidiarrheal treatment (before baseline or during the study period), chronic or toxic diarrhea and impossibility to follow the patient for more than 12 hours.

The patients were randomly assigned to receive xyloglucan and ORS and ORS alone at a ratio of 1:1. Xyloglucan (Xilaplus<sup>®</sup>, Novintethical Pharma, SA) was administered in the form of oral sachets (containing xyloglucan, gelatin of porcine origin, corn starch and magnesium stearate). ORS (Humana Electrolit Banana, Humana GmbH, Germany) was administered as powder for oral solution (containing sodium and potassium, chloride and glucose).

During the first enrolment visit (visit 0), patients from the two groups were randomized to receive a 5-day treatment (one sachet every 8 hours for children younger than 3 years and 2 sachets every 8 hours in the case of xyloglucan, while ORS was prescribed according to leaflet provisions and medical judgement), with the first dose being administered at the time of recruitment (visit 0). In order to assess adherence to treatment, parents or legal guardians recorded the use of study medication on the diary card and were instructed to return all packages of the used and unused product at visit 1 (performed 2 days after baseline) and at visit 2 (performed 5 days after baseline).

During the baseline visit, demographic, anthropometric (weight, height and body mass index –BMI-) and clinical (including vital signs, comorbidities and symptomatology of acute gastroenteritis during the previous 3 days and at the recruitment visit) were recorded. Clinical symptoms of acute gastroenteritis were assessed by patient's interview and exploration and included nausea, vomiting, anorexia, abdominal pain, flatulence, stools (type, number, duration of diarrhea, presence of blood/mucus/pus in faeces), fever, dehydration (abnormal skin turgor, weight decrease) and signs of peritonitis and/or sepsis. Consistency of stools was classified using the 7-point Bristol Stool Scale (Heaton and O'Donnell, 1994; Palsson et al, 2014).

During the baseline visit (visit 0), parents or legal guardians also received an *ad-hoc* questionnaire, included in the patient's daily diary, to assess the consistency of stools and diarrheal symptoms (both objective and subjective) at 1, 3, 6, 12 and 24 hours following the first dose administration. Stools emissions (including number of emissions/day), with mucus and/or blood, were recorded and consistency of each stool was assessed using the 7-point Bristol Stool Scale (type 1 corresponds to separate hard lumps, like nuts while type 7 corresponds to watery, no solid pieces, entirely liquid) (Heaton and O'Donnell, 1994; Palsson et al, 2014). The presence of subjective symptoms such as nausea, vomiting (including number of vomits/day), abdominal pain and flatulence was also recorded in the *ad-hoc* questionnaire.

At visit 1 (which took place 48 hours after baseline) and visit 2 (which took place 5 days after baseline) the investigators reviewed the patient's daily diary. During these visits, symptoms and clinical signs were recorded and symptoms assessment was also performed by patient's interview and exploration.

Occurrence of adverse events was assessed in all study visits and by phone calls (performed 10 days after study completion). All these data were transferred into the electronic patient's case report form (eCRF).

The primary efficacy variable was the variation in the number of type 7 stools and type 6 and 7 stools during the 5-day treatment and the rapidity of action of the studied products in the intention-to-treat (ITT) population, defined as all randomized patients who had at least one post-treatment measurement.

The primary safety variable was the prevalence of adverse events in both groups of patients in the safety population, defined as all patients who received at least one dose of the studied product.

Sample size ( $n = 36$ ,  $n = 18$  in each group) was calculated to have a 80% power to show, with 95% probability, differences in the evolution of the number of type 6 and 7 stools during the study period.

Descriptive analyses (within-patient  $n$ , mean, median, standard deviation, minimum and maximum) were performed for quantitative variables and frequency counts by category were calculated for qualitative variables. Following the results of normality tests (Kolmogorov-Smirnow test), data obtained at the three visits (baseline, 2 and 5 days) were compared by means of Friedman's Anova and Kendall's coefficient of concordance for non-parametric dependent data. Comparisons of data obtained at a certain visit between the two treatments were performed by means of Mann-Whitney U test for non-parametric and independent data. Two-sided  $p$ -values were obtained and statistically significant results were declared if  $p < 0.05$ . Statistical analyses were performed using IBM SPSS 19 software for Windows.

## RESULTS

A total of 36 patients were included in the study (18 in each group). All randomized patients had at least one post-treatment measurement and received at least one dose of the product, thus the ITT and safety populations coincided.

Table 1 shows the demographic and clinical characteristics of patients. In the whole sample, 58.3% of girls were included. In the active group, there was the same number of girls as the boys (50.00%;  $n = 9$ ), while, in the control group, a higher number of girls was included (66.67%;  $n = 12$ ) (Table 1).

Mean age of children was  $4.33 \pm 3.80$  years ( $4.72 \pm 4.33$  in the active group and  $3.94 \pm 3.26$  in the control group) (Table 1). By age ranges, the most prevalent group was 1 – 5 years old (38.89% in the active group; 55.56% in the control group; 47.22% in the whole sample), followed by the 5 – 10 years range (22.22% vs 27.78%; 25.00% in the whole sample) and > 10 years (22.22% vs 5.56%; 13.88% in the whole sample) and  $\leq 1$  year ranges (16.67% vs 11.11%; 13.88% in the whole sample) (Table 1).

At baseline, a majority of patients had normal hydration status (61.11% vs 72.22%) and the rest presented mild dehydration, while a majority of patients in both groups had fever, with temperatures ranging from 37 to 38°C (27.78% vs 33.33%) and higher than 38°C (22.22% vs 27.78%) (Table 1).

Vital signs, including heart rate, blood pressure and breath rate, were within the normal values in all patients, while no relevant comorbidities were present.

During the first 6 h of treatment, the group treated with xyloglucan and ORS showed a faster onset of action and improvement of diarrheal symptoms, measured as absolute number of type 7 stools, compared with the control group. Accordingly, in the active group the highest reduction of the number of type 7 stools was observed at 6 hours (active group: 48 stools at baseline to 2 stools at 6 hours; control group: 48 stools at baseline to 8 stools at 6 hours), with an effect that was statistically significant compared with the control group ( $p = 0.027$ ) (Figure 1A). The same significant difference was observed considering the evolution of the mean number of type 7 stools (active group: from 2.67 to 0.11; control group: from 2.67 to 0.44).

Considering type 6 and 7 stools, we observed a more pronounced reduction in the group treated with xyloglucan and ORS in comparison with the control group, in terms of absolute number of type 6 and 7 stools (Figure 1B) and mean number of type 6 and 7 stools (Figure 1C). In the active group, the number of type 6 and 7 stools decreased from 93 stools at baseline to 68 at day 1, 10 at day 2 and 2 at day 3, disappearing at days 4 and 5, while in the control group at days 4 and 5, type 6 and 7 stools were still present (Figure 1B). The same trend was observed in terms of the evolution of mean number of type 6 and 7 stools (Figure 1C) and also considering the percentage of patients with type 6 and 7 stools in each study visit (Figure 1D). In comparison with the control group, the percentage of patients with type 6 and 7 stools was always lower in the active group from day 1 to day 5, being statistically significant at days 3 ( $p = 0.026$ ; Pearson's Chi-squared test) and 5 ( $p = 0.034$ ; Pearson's Chi-squared test) (Figure 1D).

A trend to higher effect of xyloglucan and ORC in reducing the percentage of patients with nausea was observed throughout the study period, although no statistically significant differences were observed in comparison with the control group. We note that in the active group, the percentage of patients without nausea was achieved as early as after 24 hours, while in the control group disappearance of nausea was reached at 72 h post-baseline (Figure 2A). Similarly, the disappearance of vomiting occurred earlier in the active group (after 24 hours) (Figure 2B).

We also noted an earlier reduction in the percentage of children with abdominal pain (Figure 2C) and also with flatulence (Figure 2D).

Both treatments were safe and well tolerated, with no adverse events being reported during the study period.

## DISCUSSION

Rehydration is the key treatment of acute gastroenteritis in children and should be applied as soon as possible (Guarino et al, 2008) to avoid risks and complications, as life-threatening dehydration, electrolyte disturbances, disturbed digestion and absorption of nutrients with nutritional deterioration, leading to the need of enteral/parenteral rehydration and the consequent hospitalization (Ciccarelli et al, 2013; Wittenberg, 2012; Guarino et al, 2014).

For this reason, those interventions that can increase the efficacy of ORS deserve special consideration.

In the present study, we have demonstrated that ORS administrated in combination with xyloglucan produced a significant reduction of the most dehydrating stools (type 6 and 7), in comparison with ORS alone, as early as 6 hours post-treatment. This faster onset of action supports the use of this combination to avoid dehydration in children and the associated complications.

These results are also in line with the findings obtained in a previous randomized clinical trial in adults with acute diarrhea, in which, during the first 24 h of treatment, the xyloglucan group showed a faster onset of action and improvement of diarrheal symptoms, measured as absolute number of type 6 and 7 stools, compared with the diosmectite and *S. bouliardii* groups. Accordingly, in the xyloglucan group the highest reduction of the number of type 6 and 7 stools was observed at 6 hours with an effect that was statistically significant compared with diosmectite group ( $p = 0.031$ ) (Gnessi et al, 2015, submitted; Gnessi et al, 2015 UEG week congress).

It seems clear, therefore, that xyloglucan, in both children and adults, is able to stop dehydration by rapidly reducing the number of dehydrating stools. These results are also in line with finding from *in vitro* and *in vivo* studies, in which xyloglucan generated a pH resistant biopolymer onto intestinal epithelial cells with anti-absorptive properties. By glending xyloglucan with natural gelatine type A, the film improved the absorptive properties, forming a physical barrier that counteracted the effects of microorganisms translocation and toxins by means of the reinforce of trans-epithelial electrical resistance (TEER). In that way, xyloglucan reduced significantly the damage of tight junctions and the trigger of the inflammatory immune response (Bueno et al, 2014; Sekkal et al, 2015 in preparation).

Altogether, these results support the use of xyloglucan and other film-forming agents of this mucosal protectors family for the management of disease that are accompanied by diarrhea, as in the case of gastroenteritis in children.

In fact, in an observational study in 239 children (aged from 3 months to 12 years) with acute diarrhea with two cohorts (treated with ORS alone and treated with ORS plus another film-forming agent, gelatin tannate), a statistically significant reduction in the number of stools was observed at 12 hours post-treatment in patients treated with the combination, in comparison with patients treated with ORS alone (Esteban et al, 2009).

In a recent case report of a 4.5-month-old baby girl with a 2-day history of watery diarrhea and fever due to rotavirus gastroenteritis, the administration of the film-forming agent in combination with intravenous fluid therapy was able to considerably improve child's diarrhea improved within the first twelve hours and resolved completely within three days (Guzganu, 2012).

Therefore, to date, it seems that there is enough data to support the use of these film-forming agents to stop diarrhea, particularly in the pediatric population, in combination with ORS.

Moreover, as already reported in adults (Gnessi et al, 2015 submitted; Gnessi et al, 2015 UEG week congress), xyloglucan showed a trend to improve other related symptoms as nausea, vomiting or abdominal pain, probably due to the favourable effects on the intestinal mucosa.

Finally, no adverse events were recorded during the study, thus supporting the safety profile of this family of agents.

In conclusion the administration of xyloglucan in combination of ORS is an efficacious and safe option in the clinical practice for the treatment of acute diarrhea in the pediatric population, with a rapid onset of action in reducing dehydrating stools. The results obtained in this study support the use of xyloglucan added to ORS in children with acute gastroenteritis.

**COMPETING INTERESTS:**

Núria Piqué received honoraria from Novintethical, SA to write the article.

Catalin Pleasea Condratovici has no conflict or competing interest with Novintethical SA.

Vladimir Bacarea has no conflict or competing interest with Novintethical SA and was an independent Biostatistician selected by the CRO.

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## REFERENCES

Bueno L, Theodorou V, Sekkal S. Xyloglucan: a new agent to protect the intestinal mucosa and to prevent bacterially-mediated alteration of tight junction permeability. Abstract P1675. 22<sup>nd</sup> United European Gastroenterology (UEG) week. Vienna; 2014. October 18-22.

Ciccarelli S, Stolfi I, Caramia G. Management strategies in the treatment of neonatal and pediatric gastroenteritis. *Infect Drug Resist.* 2013 Oct 29;6:133-61. doi: 10.2147/IDR.S12718.

Dickinson B, Surawicz CM. Infectious diarrhea: an overview. *Curr Gastroenterol Rep.* 2014 Aug;16(8):399. doi: 10.1007/s11894-014-0399-8.

Esteban J, Durbán F, López-Argüeta S, López J. A comparative analysis of response to ORS (oral rehydration solution) vs ORS + gelatin tannate in two cohorts of pediatric patients with acute diarrhea. *Revista Española de Enfermedades Digestivas* 2009;101(1):41-48.

Franceschi F, Scaldaferrì F, Riccioni ME, Casagrande I, Forte E, Gerardi V, Cordischi C, Antonini S, Tortora A, Di Rienzo T, D'angelo G, Merra G, Costamagna G, Zuccalà G, Gasbarrini A: Management of acute diarrhea: current and future trends. *Eur Rev Med Pharmacol Sci* 2014,18:2065-2069.

Gnessi L, Bacarea V, Marusteri M, Piqué N. Xyloglucan for the treatment of acute diarrhea: results of a randomized, controlled, open-label, parallel group, multicentre, national clinical trial. *BMC Gastroenterology*. Submitted.

Gnessi L, Llop X, Piqué N. Xyloglucan for the treatment of acute diarrhea: results of a randomized, controlled, open-label, parallel group, multicentre, national clinical trial. UEG week 2015. Barcelona, October 24-28, 2015.

Guarino A, Albano F, Ashkenazi S, Gendrel D, Hoekstra JH, Shamir R, Szajewska H; ESPGHAN/ESPID Evidence-Based Guidelines for the Management of Acute Gastroenteritis in Children in Europe Expert Working Group. European Society for Paediatric Gastroenterology, Hepatology, and Nutrition/European Society for Paediatric Infectious Diseases evidence-based guidelines for the management of acute gastroenteritis in children in Europe: executive summary. *J Pediatr Gastroenterol Nutr.* 2008 May;46(5):619-21.

Guarino A, Ashkenazi S, Gendrel D, Lo Vecchio A, Shamir R, Szajewska H. European society for pediatric gastroenterology, hepatology, and nutrition/european society for pediatric infectious diseases evidence-based guidelines for the management of acute gastroenteritis in children in europe: update 2014. *J Pediatr Gastroenterol Nutr.* 2014 Jul;59(1):132-52.

Guzganu IL. Severe diarrhea in a 4-month-old baby girl with acute gastroenteritis: a case report and review of the literature. *Case Rep Gastrointest Med.* 2012;2012:920375. doi: 10.1155/2012/920375. Epub 2012 Mar 25.

Heaton KW, O'Donnell LJ: An office guide to whole-gut transit time. Patients' recollection of their stool form. *J Clin Gastroenterol* 1994;19:28–30.

O'Ryan G M, Ashkenazi-Hoffnung L, O'Ryan-Soriano MA, Ashkenazi S. Management of acute infectious diarrhea for children living in resource-limited settings. *Expert Rev Anti Infect Ther.* 2014 May;12(5):621-32.

Palsson OS, Baggish J, Whitehead WE: Episodic nature of symptoms in irritable bowel syndrome. *Am J Gastroenterol* 2014,109:1450-1460.

Ruszczynski M, Urbańska M, Szajewska H: Gelatin tannate for treating acute gastroenteritis: a systematic review. *Ann Gastroenterol* 2014,27:121-124.

Xyloglucan: a new agent to protect the intestinal mucosa and to prevent bacterially-mediate alteration of tight junction permeability.

Sekkal S, Theodoru V, Llop X, Bueno L. Xyloglucan: a new agent to protect the intestinal mucosa and to prevent bacterially-mediate alteration of tight junction permeability. In preparation.

Vandenplas Y, De Greef E, Hauser B, Devreker T, Veereman-Wauters G. Probiotics and prebiotics in pediatric diarrheal disorders. *Expert Opin Pharmacother.* 2013 Mar;14(4):397-409.

Wittenberg DF. Management guidelines for acute infective diarrhoea/gastroenteritis in infants. *S Afr Med J.* 2012;102:104–107.

## TABLES

**Table 1. Demographic and antropometric characteristics of children.**

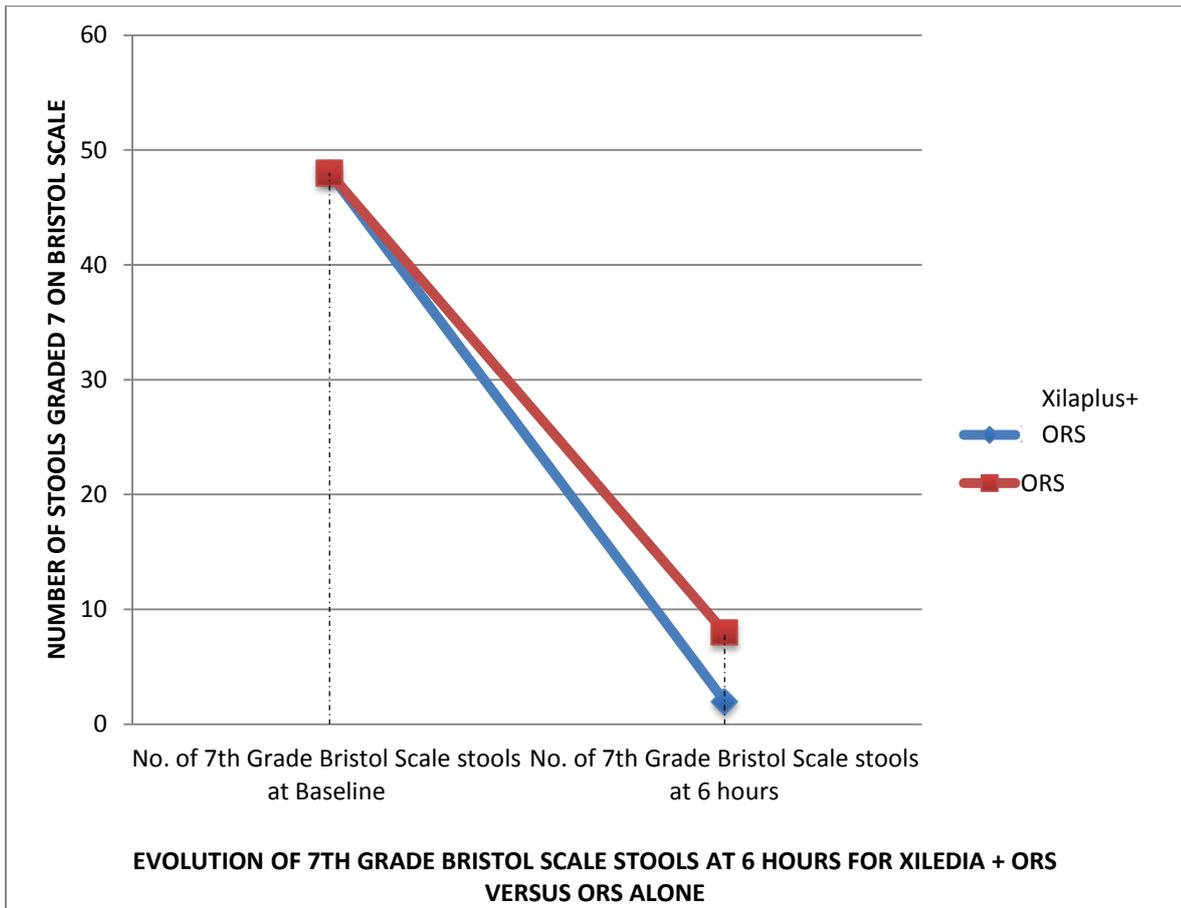
	<b>Statistical variable</b>	<b>Xyloglucan +ORS</b>	<b>ORS</b>	<b>Total</b>
Gender (Girls)	n (%)	9 (50.00)	12 (66.67)	21 (58.33)
Age (years)	Mean (SD)	4.33 (3.80)	4.72 (4.33)	3.94 (3.26)
Age ranges	n (%)			
≤ 1 year		3 (16.67)	2 (11.11)	5 (13.88)
1 – 5 years		7 (38.89)	10 (55.56)	17 (47.22)
5 – 10 years		4 (22.22)	5 (27.78)	9 (25.00)
>10 years		4 (22.22)	1 (5.56)	5 (13.88)
Hidration status	n (%)			
normal		11 (61.11)	13 (72.22)	24 (66.66)
Mild dehydration		7 (38.89)	5 (27.78)	12 (33.33)
Body temperature				
≤37°C		9 (50.00)	7 (38.89)	16 (44.44)
37 – 38°C		5 (27.78)	6 (33.33)	11 (30.55)
>38°C		4 (22.22)	5 (27.78)	9 (25.00)

SD: standard deviation

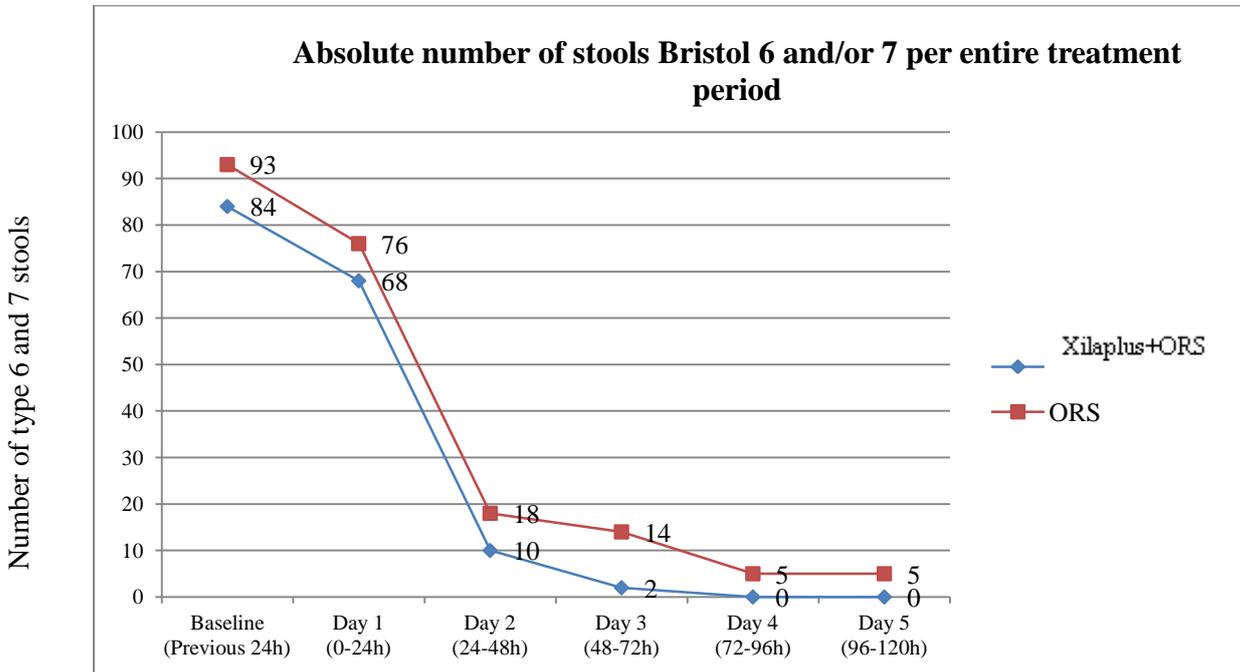
**FIGURES**

**Figure 1. Evolution of dehydrating stools in both groups. A) Evolution of the absolute number of type 7 stools during the first 6 hours. B) Evolution of absolute number of type 6 and 7 stools during the study period. C) Evolution of mean number of type 6 and 7 stool during the study period. D) Evolution of the percentage of patients with type 6 and 7 stools during the study period.**

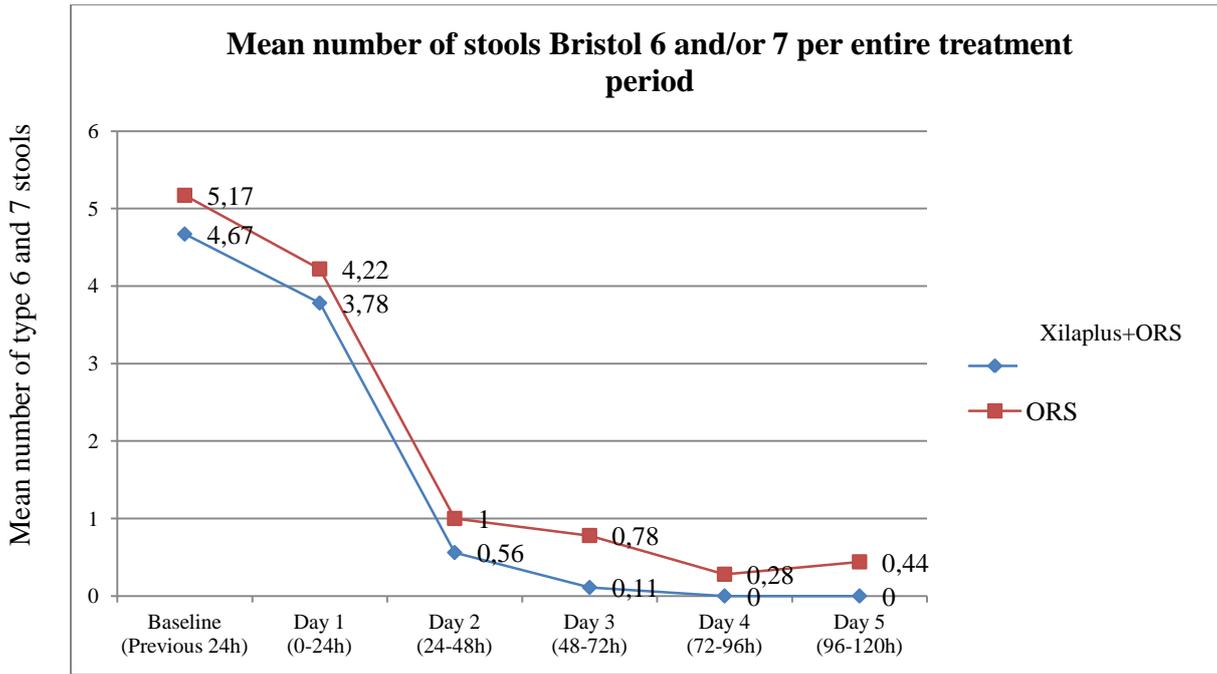
A)



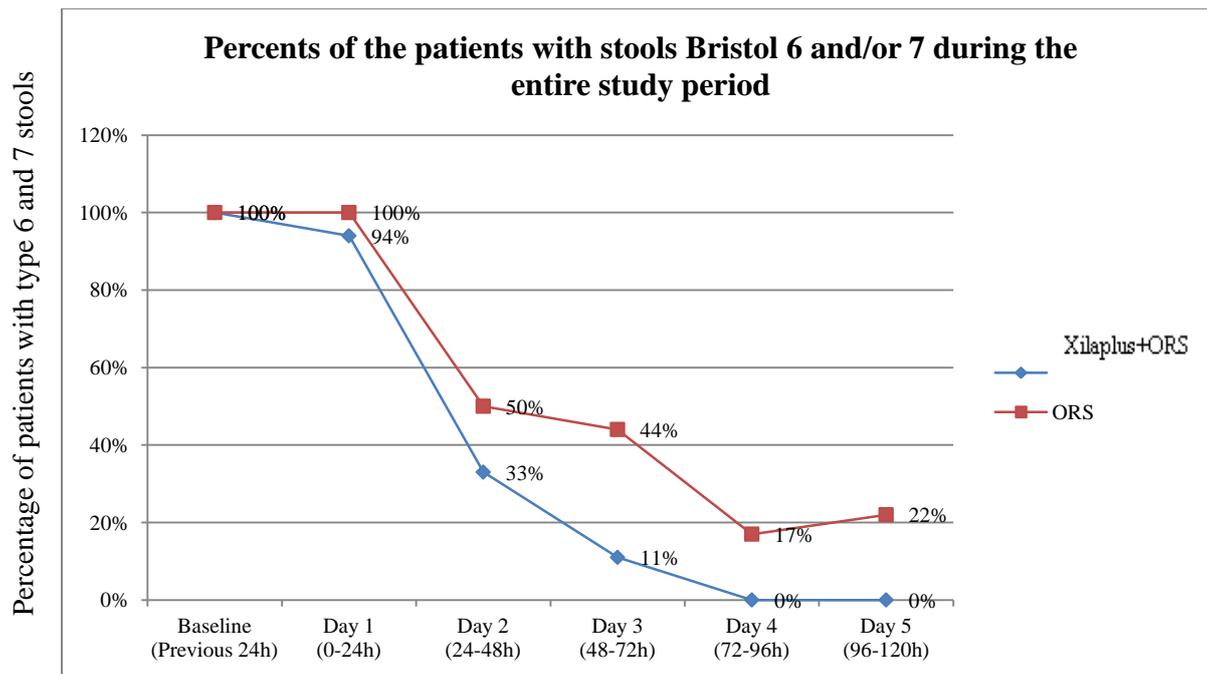
B)



C)

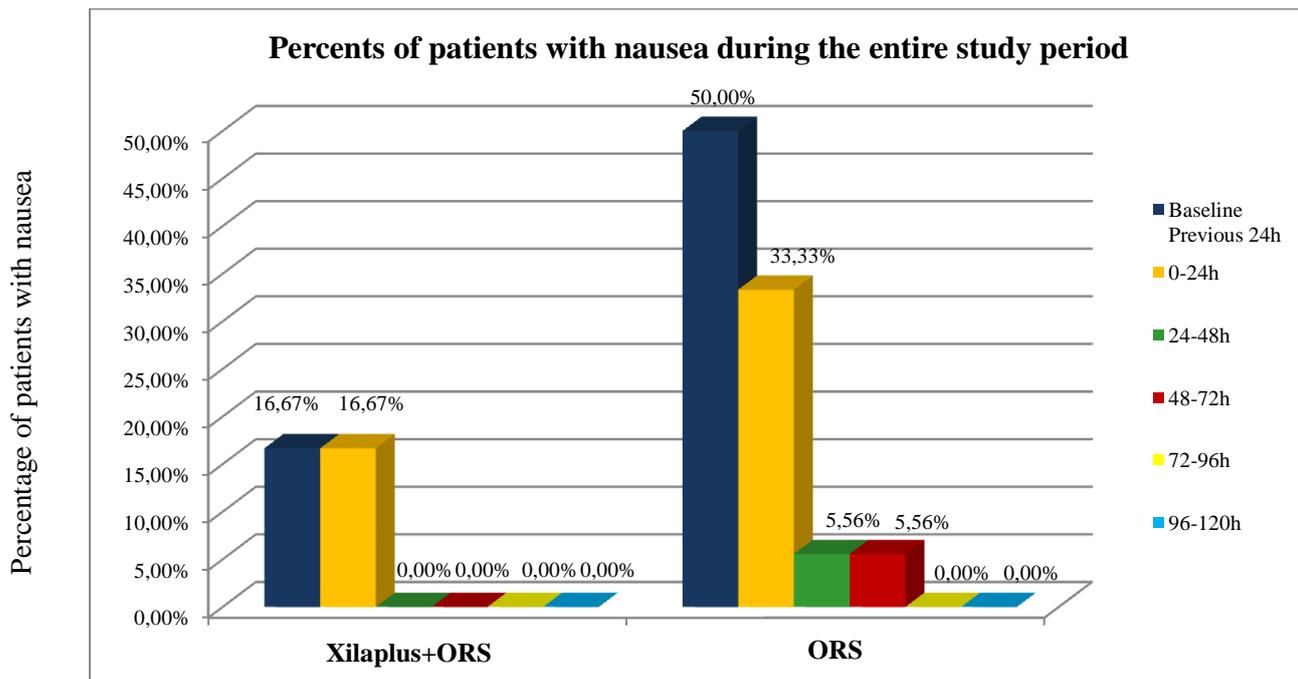


D)

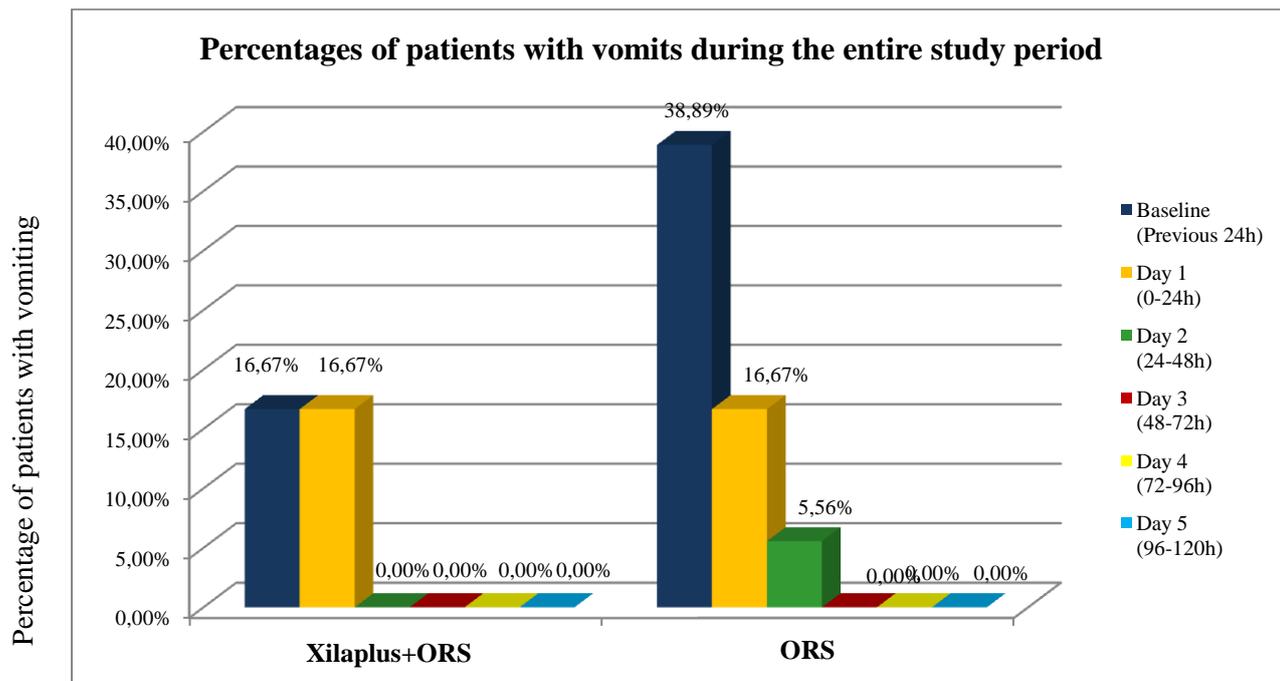


**Figure 2. Evolution of clinical symptoms of gastroenteritis during the study period in both groups. A) Evolution of the percentage of patients with nausea. B) Evolution of the percentage of patients with vomiting. C) Evolution of the percentage of patients with abdominal pain. D) Evolution of the percentage of patients with flatulence.**

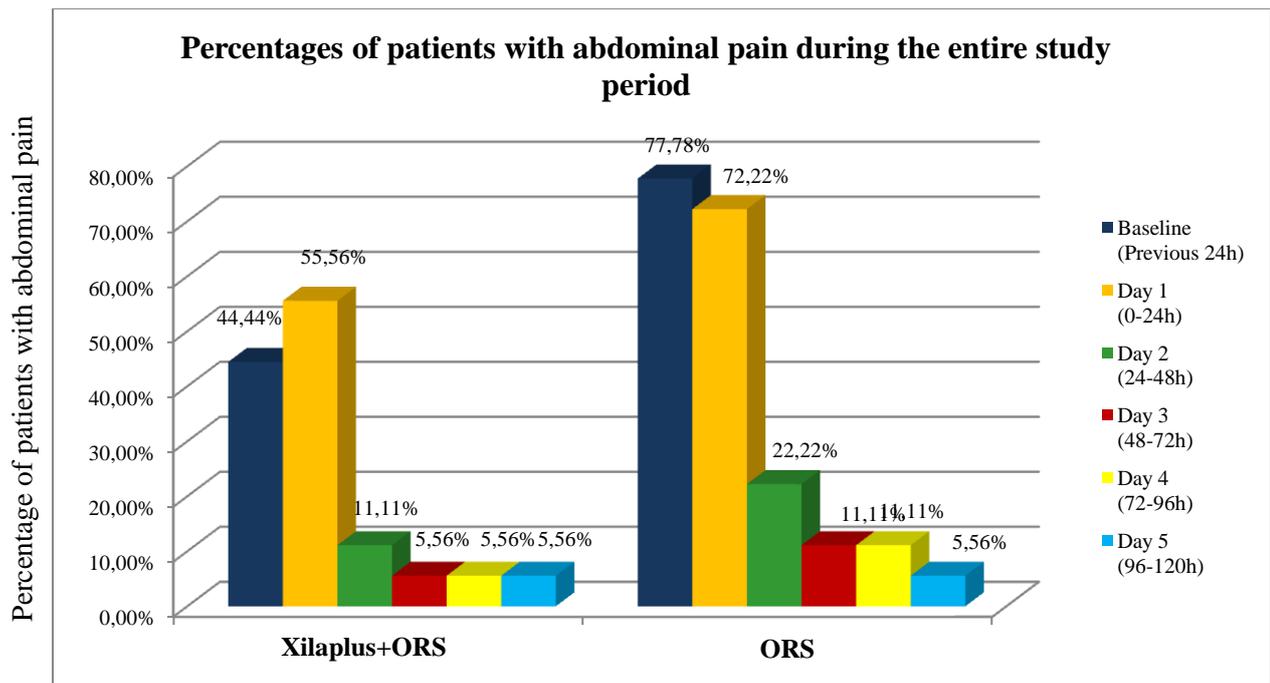
**A)**



**B)**



C)



D)

