


Randomized, direct comparison study of *Saccharomyces boulardii* CNCM I-745 versus multi-strained *Bacillus clausii* probiotics for the treatment of pediatric acute gastroenteritis

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Abstract

Background: The choice of an appropriate probiotic for pediatric acute gastroenteritis (PAGE) can be confusing. Our aim was to compare the efficacy and safety of 2 probiotics (*Saccharomyces boulardii* CNCM I-745 vs a 4-strain mixture of *Bacillus clausii* O/C, SIN, N/R, T) for the treatment of PAGE.

Methods: A 2-arm parallel, randomized trial recruited children (6 months to 5 years old) with mild-moderate acute diarrhea, from 8 centers in Argentina. A total of 317 children were enrolled and blindly randomized to 5 days of either *S. boulardii* CNCM I-745 (n = 159) or a 4-strain mixture of *B. clausii* (n = 158), then followed for 7 days post-probiotic treatment. A stool sample was collected at inclusion for pathogen identification. The primary outcome was duration of diarrhea defined as the time from enrollment to the last loose stool followed by the first 24-hour period with stool consistency improvement. Secondary outcomes included frequency of loose stools/day, severity of diarrhea, number reporting no diarrhea at Day 6, time-to-first formed stool, recurrence of diarrhea by study end (Day 12) and safety outcomes.

Results: Three hundred twelve (98%) children completed the study. *S. boulardii* CNCM I-745 showed a significant reduction ($P = .04$) in the mean duration of diarrhea (64.6 hours, 95% confidence interval [CI] 56.5–72.8) compared to those given *B. clausii* (78.0 hours, 95% CI 69.9–86.1). Both probiotics showed improvement in secondary outcomes and were well-tolerated.

Conclusion: In this study, *S. boulardii* CNCM I-745 demonstrated better efficacy than *B. clausii* mix for reducing the duration of pediatric acute diarrhea.

Abbreviations: APP = as-per-protocol, CI = confidence interval, ITT = intent-to-treat, ORS = oral rehydration solution, PAGE = pediatric acute gastroenteritis, RCT = randomized controlled trials.

Keywords: *Bacillus clausii*, diarrhea, gastroenteritis, probiotics, *Saccharomyces boulardii*.

1. Introduction

Pediatric acute gastroenteritis (PAGE) is a leading cause of morbidity and mortality in children under 5 years old, especially in developing countries and has significant impact on the physical and emotional well-being of the child and their parents.^[1–3] Parents of children with PAGE have multiple concerns ranging

from fear their child might suffer significant dehydration and discomfort, to the parent's inability to rapidly relieve the symptoms, to problems administering oral rehydration solution (ORS), to the disruptive effects of this illness on parental sleep, work, and household routines.^[4]

Current international recommendations for treatments for PAGE include oral rehydration, continuing oral feeding,

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The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the third party.

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anti-infective drugs (if etiology is determined) and some recommend probiotics.^[5,6] Probiotics are living microbes that have a health benefit on a host when given in adequate doses.^[7] But not all probiotic strains are effective for PAGE, as the efficacy has been found to be both strain-specific and disease-specific.^[8] Choosing an appropriate probiotic for PAGE may be challenging and depends upon several factors: the ability of the strain or strains to restore the disrupted microbiome found in PAGE,^[9–11] availability of the high-quality probiotic product in the child's country,^[12] and a consensus of which probiotic strains have sufficient evidence for efficacy and safety.^[13] Recent meta-analyses and systematic reviews using data pooled from randomized, controlled trials (RCTs) found 3 types of probiotics (*Saccharomyces boulardii* CNCM I-745, *Lactobacillus rhamnosus* GG and *Lactobacillus reuteri*) are efficacious for the treatment of PAGE, but recommendations for the 4-strain mixture (*Bacillus clausii* O/C, SIN, N/R, T) are conflicting.^[6,14–17] A consensus on which probiotic strains to use has been hampered by the heterogeneity present in these pooled RCTs due to differences in study populations, geographic location, and etiology of the PAGE, among other factors.^[6] Direct “head-to-head” comparisons with 2 different probiotics tested within the same study population and geographic area may help to decide which probiotic is best, but this has been infrequently conducted.^[18–21]

The aim of this study is to directly compare 2 different widely available probiotics to provide evidence-based recommendations to health care providers for the treatment of PAGE.

2. Methods

2.1. Study design

The SABINA (*S. boulardii* in children in Argentina) study was a 2-arm parallel, randomized trial. Outpatient children seen for mild-moderate acute diarrhea were recruited from 8 private pediatric practices in Argentina. Consolidated standards for reporting trials guidelines were followed for this study (see Table S1, Supplementary Digital Content 1, <http://links.lww.com/MD/H250> which lists the consolidated standards for reporting trials checklist items).^[22]

2.2. Ethics

The study was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonization Good Clinical Practices guidelines. Informed consent was obtained from the child's parent prior to enrollment. The study was approved by the research ethics committees at each study site and the study was registered with the Clinical Trials Registry (Clinicaltrials.gov: NCT03539913 [May 30, 2018]).

2.3. Participants

The patients were brought to medical centers by their parents because of the occurrence of acute onset of diarrhea. Before entering the patients into this clinical study, the investigators were asked to perform a complete examination of the patient and conduct an interview of the parents including about medical history, recent travel, recent vaccination, previous treatments intake, modification in food habits or in child behavior. This screening step allowed investigators to exclude other underlying causes of acute diarrhea, such as antibiotic intake or other reasons listed above. The investigators were then able to judge if the patient was suffering from PAGE, as defined by the World Health Organization.^[1] Inclusion criteria included: children (6 months to 5 years old) presenting with acute diarrhea. Exclusion criteria included: inability to take oral medications, >50% breast-fed, severe malnutrition, severe dehydration requiring intravenous rehydration, chronic underlying disease such as

systemic infection, severe gastrointestinal disorder or immunocompromised, treatment with systemic antibiotics or antifungal agents within 2 weeks, motility-altering medications such as laxatives, antiemetics, antisecretory or adsorbent medications, opiates, etc, within 1 week, probiotic or prebiotic within 1 week, known hypersensitivity to probiotics, or contra-indications to probiotic administration (such as central venous catheter use) or concurrent participation in another clinical trial.

2.4. Definitions of PAGE

PAGE was diagnosed as children presenting with acute diarrhea (3 or more loose or liquid stools in a 24-hour period) within the previous 24 hours but for less than 5 days, based on the WHO definition of PAGE and other standard guidelines.^[1,23] Loose-liquid stools were defined using the Bristol stool scale.^[24] The severity of PAGE at admission and during the course of the study was defined using the Modified Vesikari Score, a validated acute gastroenteritis severity scale in children populations.^[23,24] Scores from 0 to 8 reflect a mild illness, from 9 to 10 reflect a moderate illness and ≥ 11 reflect a severe illness. The modified Vesikari instrument has a total 20-point score and contains 7 equally weighted variables: duration of diarrhea and vomiting, maximal number of diarrheal stools and vomiting episodes per 24-hour period, highest fever reading, health care provider visits and administered treatments (see Table S2, Supplementary Digital Content 2, <http://links.lww.com/MD/H251> which describes the factors measured in this tool).

2.5. Randomization

Children were blindly randomized into 1 of 2 groups: *S. boulardii* CNCM I-745 or the 4-strain probiotic mixture (*B. clausii* O/C, SIN, N/R, T) stratified on site, using random block design. The randomization list was generated by an independent contract research organization (Theradis Pharma, Cagnes-sur-Mer, France) using random number generator software (1:1 allocation ratio).

2.6. Study interventions

The study intervention probiotics were either *S. boulardii* CNCM I-745 (Floratil®, Biocodex, France) in sachets (250 mg) or a 4-strain mixture of *B. clausii* O/C, SIN, N/R, T (Enterogermina®, Sanofi, Laboratoire Unither, France) in 5 mL vials containing 2×10^9 spores. Dosage used in the study were the ones indicated in the SmPC/package insert of the 2 products: 1 sachet (250 mg) twice daily for *S. boulardii* CNCM I-745 (i.e., total colony forming units per day (cfu/d) was 1×10^{10} cfu/d) and 1 vial twice daily for *B. clausii* O/C, SIN, N/R, T (i.e., 4×10^9 cfu/d). Both study medications were given for 5 days. As recommended by European guidelines for PAGE, ORS sachets were offered during the study.^[23]

Study medication boxes were prepared by Theradis Pharma according to the randomization list and consecutive study numbers assigned. The sealed study medication boxes were identical in exterior appearance, tamper-proof and equal in weight so that the allocation of the study medication was blinded (physician and parents). Blocks of study boxes were sent to each site to be assigned in ascending order as they were enrolled. Once the study medication boxes were opened, the different formulations (sachet or vials) unblinded the treatment. The first dose of treatment was taken during the enrollment consultation.

2.7. Data collection

Data was collected in daily diaries completed by parents (diarrheal symptoms, adverse reactions and study doses taken) and verified in case report forms by study investigators during daily

telephone interviews during the first 5 days. A 7-day follow-up period without treatment was done to document any recurrences of diarrhea or delayed adverse reactions. A stool sample was collected at enrollment and analyzed for routine intestinal pathogens.

2.8. Statistical analysis

2.8.1. Sample size calculation. Sample size determination based on the following assumptions was made to detect a difference in mean duration of diarrhea of at least 12 hours: a standard deviation of 36 hours, a power of 80% and a 2-sided significance level of $\alpha = 5\%$. It was calculated that at least 286 children would be required for this trial.

2.8.2. Primary outcome. The primary analysis was done using an intent-to-treat (ITT) analysis including all eligible children who received at least 1 dose of study medication and had at least 1 diarrhea outcome assessment during the study. The primary outcome was assessed using an analysis of covariance model comparing the mean adjusted duration of diarrhea (hours) between treatment groups. The model included treatment and center as fixed classification effects and age (years) and time since start of diarrhea at Day 1 (days) as baseline covariates. The outcome is reported as Least Square adjusted means (LS Means with 95% confidence interval [CI]) and used a 2-sided significance level at $P < .05$. The unadjusted mean diarrhea durations were also calculated for each probiotic to assess the impact of adjusting the factors described above. The primary outcome was also assessed as time to event endpoint using Kaplan–Meier methodology and associated log-rank test.

2.8.3. Sensitivity analyses. Sensitivity analyses of diarrhea duration was done on 3 parameters (the total diarrheal duration, the etiology of diarrhea and an As-Per-Protocol (APP) analysis. Sensitivity analyses were done assessing the total duration of diarrhea (from day of initial diarrheal onset prior to enrollment to the day of diarrhea cessation or study end) for each probiotic group. The mean duration of diarrhea was also analyzed using APP analysis, which excluded study participants with major protocol violations (lost to follow-up, <80% compliance with study medication, exclusion medication taken (antidiarrheal or antibiotics), incorrect study medication given, withdrawal of consent or no defined diarrhea on day of enrollment).

2.8.4. Secondary analyses. Analysis of binary secondary outcome endpoints (such as number reporting recovery by Day 6) was performed using Fisher exact test or Chi-squared tests. The statistical analyses were performed using SAS® software v9.4 (SAS Institute, Cary, NC).

2.9. Outcome assessments

The primary endpoint was the mean duration (hours) of acute diarrhea, defined as the time from first intake of study treatment up to the time of diarrheal cessation. Diarrheal cessation was defined as the first calendar day with only soft-solid stools (types 1–5 on Bristol Stool Score scale).^[24] Secondary outcomes included the frequency of children with loose stools on Day 6, severity of diarrhea on Day 6, number of loose stools on Day 6, frequency cured by Day 6, time-to-first formed stool and number of recurrences of diarrhea before Day 12. Disease severity was measured using the Modified Vesikari Score, a 20-point scale based on severity of diarrhea, vomiting, fever, required medications and number of hospital visits.^[25,26] Safety data was based on treatment emergent adverse events and was assessed in all eligible participants taking at least 1 dose of study treatment.

3. Results

3.1. Study population characteristics

A total of 317 children were screened and enrolled between June 19, 2017 and June 9, 2018, of whom 159 were randomized to *S boulardii* CNCM I-745 (*S boulardii*) and 158 to *B clausii* mixture (*B clausii*), as shown in Figure 1. A total of 312 (98%) children completed the study (4 prematurely discontinued in *S boulardii* group due to withdrawal of consent or onset of an exclusion criteria and 1 was dropped in the *B clausii* group due to a serious adverse event). For the analyses, 315 patients (157 *S boulardii*; 158 *B clausii*) were considered in the ITT and 263 in the APP analysis (133 *S boulardii*; 130 *B clausii*). Two participants were excluded on Day 1 before study medication was given.

Subject demographics and baseline characteristics of the 2 study groups were comparable (Table 1), except more participants in the *B clausii* group (89.9%) had been vaccinated for rotavirus within the prior 2 years compared to those in the *S boulardii* group (80.9%). Most (96%) were enrolled with mild diarrhea, and 4% had moderate diarrhea. During the study, half of the children received ORS ($n = 81$, 51.6% in *S boulardii* group and $n = 66$, 41.8% in the *B clausii* group).

3.2. Duration of diarrhea

3.2.1. Primary outcome efficacy. The adjusted mean duration of diarrhea was significantly reduced in the *S boulardii* CNCM I-745 group (64.61 hours, 95% CI 56.45–72.76, $P = .04$) compared to the *B clausii* O/C, SIN, N/R, T group (77.98 hours, 95% CI 69.86–86.11), as shown in Figure 2. *S boulardii* CNCM I-745 significantly reduced the mean duration of diarrhea by –11.98 hours (95% CI –0.73 to –23.22, $P = .04$), as shown in the Kaplan–Meier plot (Fig. 3). In the time to event analysis using Cox proportional model, the Hazard-Ratio also indicated *S boulardii* CNCM I-745 significantly reduced the median hours to diarrhea cessation compared to *B clausii* group (HR = 0.75, 95% CI 0.60–0.95, $P = .02$). The effect of adjusting for study center, age and time since diarrhea onset was mild, as the unadjusted mean duration of diarrhea was similar to the adjusted means, with an unadjusted difference between the 2 groups of –13.38 hours (95% CI –1.86 to –24.89, $P = .02$).

3.2.2. Sensitivity analyses.

3.2.2.1. Total duration of diarrhea. The total duration from initial onset was also significantly shorter in the *S boulardii* group (112.2 hours, 95% CI 103.8–120.7, $P = .05$) compared to 131.4 hours (95% CI 123.0–139.9) in the *B clausii* group (Table 2).

3.2.2.2. As per protocol analysis. When 52 children with major protocol violations were excluded, 263 children were included in the APP analysis. Similar results for the mean durations of diarrhea were observed for both probiotic groups compared to the ITT analysis, with a difference of 11.86 hours between the 2 probiotic groups (95% CI 0.71–23.01, $P = .04$), as shown in Figure 2 and Table 2.

3.2.2.3. By etiologies of diarrhea. The causative etiology for the diarrhea was undetermined for the majority of study participants, thus limiting robust conclusions regarding the efficacy of the 2 probiotics by etiology. However, in the 70 cases where etiology could be determined, *S boulardii* CNCM I-745 significantly reduced the mean duration of diarrhea in those with bacterial etiologies (88.6 ± 64.7 hours, $P = .04$) compared to *B clausii* (139.9 ± 47.6 hours). The duration of diarrhea was similar for viral etiologies of diarrhea between the 2 study groups (Table 2).

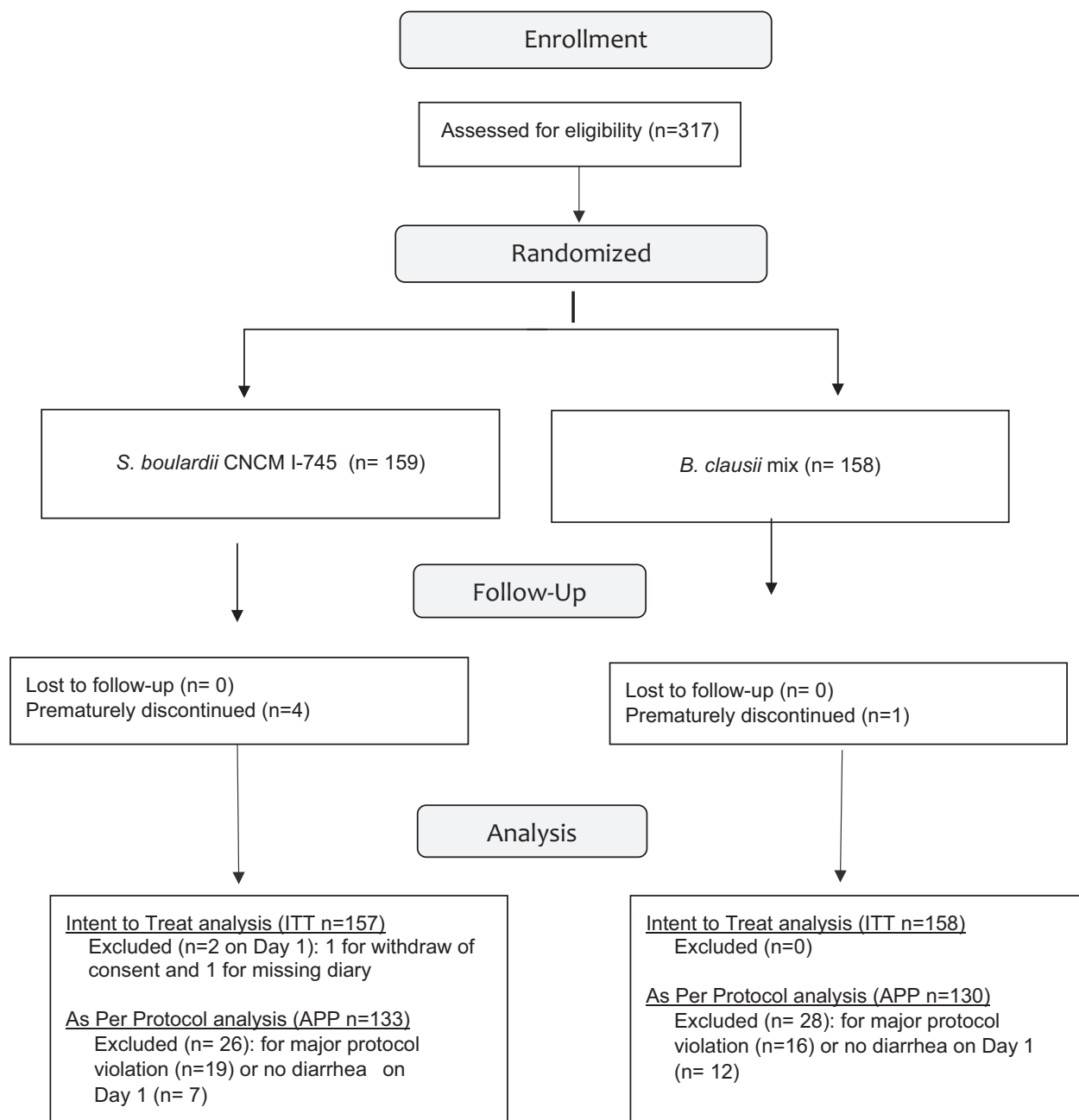


Figure 1. CONSORT flow-chart of study participants. CONSORT = consolidated standards for reporting trials.

3.3. Secondary outcomes

Both probiotics showed improvement in secondary outcomes (frequency and severity of diarrhea, time-to first formed stool and recurrences of diarrhea) as shown in Table 2. The mean frequency of stools per day on Day 6, number of children with loose stools on Day 6, number cured by Day 6, and time-to-first formed stool were similar for both probiotic groups. Recurrence of diarrhea within 7 days of follow-up was low in both *S. boulardii* (1.9%) and *B. clausii* groups (0.6%). Differences in the severity of diarrhea as assessed by the modified Vesikari scale could not be determined, as 96% of the diarrhea was classified as mild and only 12 participants had moderate diarrhea symptoms at inclusion.

3.4. Safety and tolerability

The mean duration of study medication taken was similar (4.4 ± 0.5 days) for those taking *S. boulardii* and (4.5 ± 0.4 days) those taking *B. clausii*. Compliance to both study treatments were very good (98.5% in *S. boulardii* group and 99.3% in *B. clausii* group).

The frequency of adverse events was low (6, 3.8% in *S. boulardii* and 9, 5.7% in *B. clausii* group) and of similar types (see Table S3, Supplementary Digital Content 3, <http://links.lww.com/MD/H252> which shows adverse events). Most events were mild and resolved within 1-9 days. One participant in each group reported a serious adverse event (hemolytic uremic syndrome with or without anemia), both were judged not related to the study treatments.

Table 1
Characteristics of study participants and disease symptoms at enrollment.

Characteristic	<i>Saccharomyces boulardii</i> CNCM I-745 (N = 157)	<i>Bacillus clausii</i> O/C, SIN, N/R, T (N = 158)
Gender, n (%)		
Female	67 (42.7)	72 (45.6)
Age		
Mean ± SD (mo)	26.8 ± 15.5	24.0 ± 14.2
Range (mo)	6.2-69.9	6.0-71.3
Body weight		
Mean ± SD (kg)	12.8 ± 3.7	11.9 ± 3.0
Range (kg)	10.2-15.1	9.7-13.9
Breast-fed since birth, n (%)	152 (96.8)	154 (97.5)
Any medical history, n (%)*		
Infections and infestations	7 (4.5)	10 (6.3)
Respiratory disorders	2 (1.3)	2 (1.3)
Gastrointestinal disorders	3 (1.9)	0
Skin conditions	0	3 (1.9)
Congenital, familial and genetic disorders	1 (0.6)	0
Neoplasms (benign/malignant/ unspecified)	0	1 (0.6)
Diarrhea severity, n (%)†		
Mild	153 (97.5)	150 (94.9)
Moderate	4 (2.5)	8 (5.1)
Severe	0	0
Dehydration, n (%)		
None	155 (99.4)	158 (100)
Mild	1 (0.6)	0
Severe	0	0
Not reported	1	0
Nutritional status, n (%)		
Overweight/obese	2 (1.3)	0 (0)
Normal	155 (98.7)	158 (100)
Malnutrition	0 (0)	0 (0)
History rotavirus vaccination, n (%)	127 (80.9)	142 (89.9)
Time since rotavirus vaccination, mean ± SD (days)	581.9 ± 408.7	518.5 ± 365.0
Recent history diarrhea in family, n (%)	30 (19.1)	28 (17.7)
Duration diarrhea prior to Day 1, mean ± SD	1.9 ± 0.9	2.2 ± 1.0
Etiology of diarrhea, n (%)‡		
Not determined	114 (72.6)	122 (77.24)
Rotavirus	13 (8.3)	11 (6.9)
Adenovirus	7 (4.5)	10 (6.3)
<i>Shigella</i>	9 (5.7)	6 (3.8)
<i>Campylobacter</i>	6 (3.8)	2 (1.3)
<i>Salmonella</i>	4 (2.5)	2 (1.3)
<i>Escherichia coli</i> O:157	1 (0.6)	0

% = percentage, n = number of patients, SD = standard deviation.

*Any medical conditions include: infections and infestations (bronchitis, rhinitis, bronchiolitis, gastroenteritis, influenza, conjunctivitis, urinary tract infection, viral rash or laryngitis), respiratory disorders (asthma, bronchial disorder, cough), gastrointestinal disorders (gastroesophageal reflux disease or inguinal hernia), skin conditions (dermatitis), congenital, familial and genetic disorders (congenital heart disease), and neoplasms (hemangioma).

†Severity measured with Modified Vesikari Score (0–8 mild, 9–10 moderate, >11 severe).

‡Excluding no stool sample collected (n = 8) and missing data (n = 1).

4. Discussion

In this population of outpatient children with mild-moderate acute diarrhea seen at multiple private practices in Argentina, *S. boulardii* CNCM I-745 was superior to the 4-strain mixture of *B. clausii* strains in significantly reducing the mean duration of acute diarrhea by 12 hours. This appears to be clinically relevant for children and reduce concerns of parents. The superior efficacy of *S. boulardii* was robust across our sensitivity analyses, as it significantly reduced the total duration of diarrhea (from initial onset of symptoms prior to enrollment) and remained

significant after excluding protocol violators and noncompliant subjects. Interestingly, *S. boulardii* was also more efficacious for bacterial etiologies compared to *B. clausii*. The differences in efficacy may be related to the different mechanisms-of-action for these 2 probiotics. The efficacy of *S. boulardii* CNCM I-745 results from multiple mechanisms-of-action, including the ability to restore the disrupted beneficial intestinal microbiome, reduction of rotaviral-associated chloride secretion and actions against specific intestinal bacterial pathogens (e.g., *Escherichia coli*, *Salmonella*, *Campylobacter*, *Shigella*) including direct binding of the pathogen, production of anti-toxin phosphatases and proteases, interference with pathogen attachment sites on intestinal mucosa and stimulation of secretory IgA.^[9-11,27,28] While the 4-strain mixture of *B. clausii* has been shown to have immunomodulatory effects and the production of antibacterial factors, these were not documented for the intestinal bacterial etiologies causing PAGE,^[16] which may explain the lower efficacy for bacterial etiologies when compared to the *S. boulardii* strain. Other secondary outcomes for PAGE (frequency and severity of diarrhea, time-to first formed stool and recurrences of diarrhea) were slightly improved for *S. boulardii* CNCM I-745, but not statistically different than in the *B. clausii* mix.

This study confirms the superiority of *S. boulardii* CNCM I-745 over *B. clausii* found in 3 other direct comparison trials. Vineeth et al found a significant reduction in days of diarrhea for Indian children treated with *S. boulardii* CNCM I-745 (mean of 2.9 ± 0.03 days, *P* = .008) compared to those treated with the 4-strain *B. clausii* mix (mean of 3.9 ± 0.6 days).^[20] Reddy et al also found a significant reduction in Indian children with *S. boulardii* compared to *B. clausii* (3.4 ± 0.5 days and 4.3 ± 0.5 days, respectively, *P* = .001).^[21] Asmat et al also found more Pakistani children treated with *S. boulardii* were cured (45%) compared to *B. clausii* (26%), but no data on duration of diarrhea was provided.^[19]

The choice of an appropriate probiotic can be challenging due to differences in availability, cost, varying quality and differences in efficacy.^[12,13] In addition, RCTs for PAGE have used different outcome measures and study populations, making firm conclusions difficult.^[29,30] International guidelines recommend the use of 4 probiotics (*S. boulardii* CNCM I-745, or *L. rhamnosus* GG, or *L. reuteri* DSM17938 or a 2-strain mixture of *L. rhamnosus* 19070 and *L. reuteri* DSM12246), along with ORS (if dehydrated) and zinc (if deficient), but did not recommend the use of the 4-strain *B. clausii* mixture.^[6] Li et al conducted a network meta-analysis of 21 different types of probiotics (84 studies) and concluded *S. boulardii* may be the most effective probiotic in reducing both duration of diarrhea (compared with placebo).^[31]

A strength of our study is that the trial was performed in conditions close to the real-life setting and the children were treated as outpatients, which is typical for mild-moderate cases of PAGE. In addition, the study was done with 2 probiotics available in Argentina.

Our study had several limitations. Our direct comparison clinical trial lacked a placebo or non-probiotic control group, but similar efficacies are found when placebo controls are used with the only difference is in the size of the effect. Meta-analyses of pooled data from RCTs in inpatient or outpatient children with PAGE have found both probiotics were more efficacious compared to placebo or open standard treatment controls. McFarland et al pooled studies of PAGE in India and found a significant reduction of diarrhea duration compared to placebo or no treatment controls by both *S. boulardii* (SMD = -1.9 days, *P* < .001, based on 7 RCTs) and the 4-strain *B. clausii* mix (SMD = -1.4 days, *P* = .04, based on 4 RCTs).^[17] Feizizadeh et al included 22 RCTs done in 12 different countries and found *S. boulardii* reduced the duration of diarrhea by -0.8 days.^[30] Szajewska et al included 23 RCTs in her meta-analysis of *S. boulardii* trials from 11 different countries and found children with PAGE who received no treatment (control/placebo) had an average of

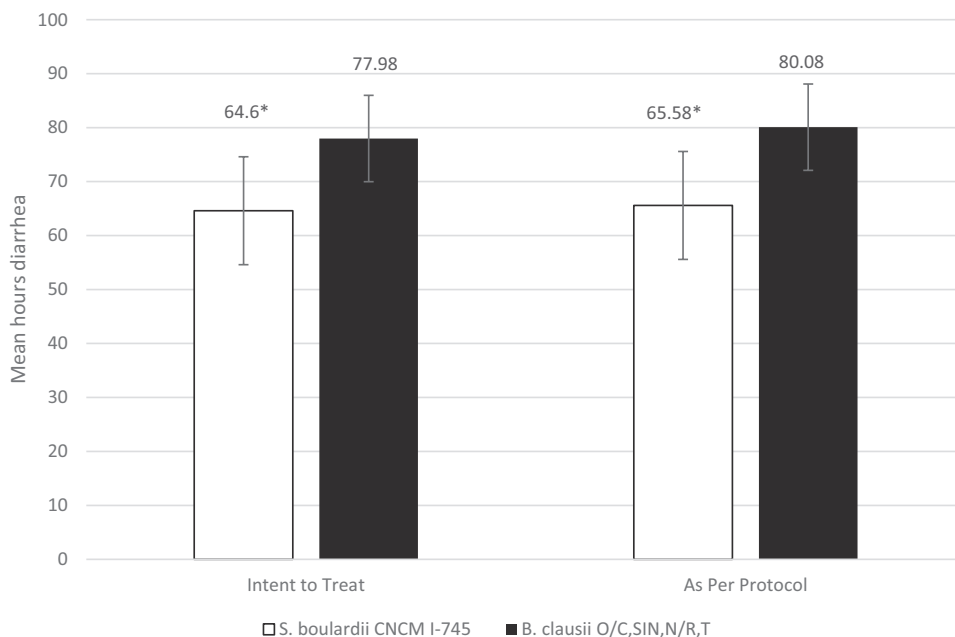


Figure 2. Adjusted mean duration of pediatric acute gastroenteritis (diarrhea by hours) by type of analysis and type of probiotic. * $P = .04$ compared to *Bacillus clausii*.

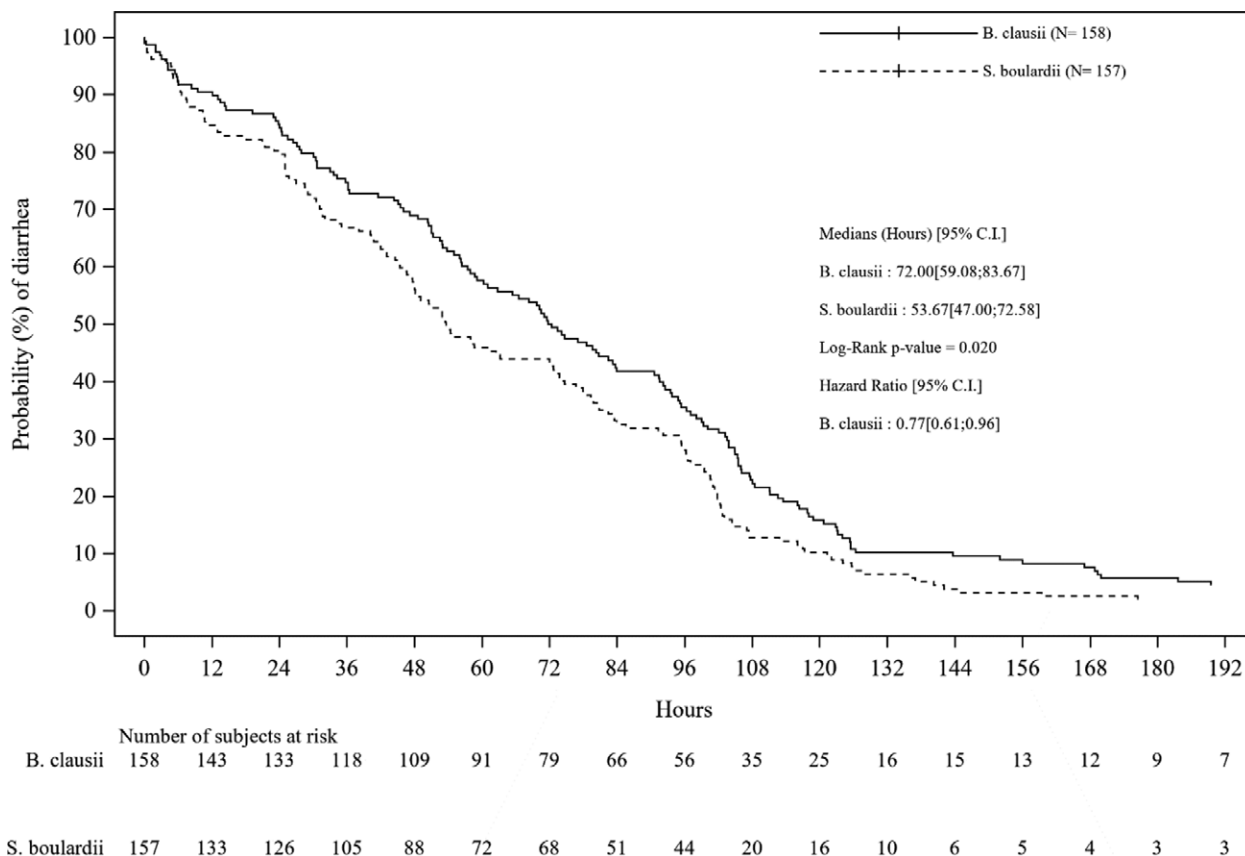


Figure 3. Kaplan–Meier plot of probability of diarrhea by hours for the 2 probiotic groups (*Bacillus clausii* O/C, SIN, N/R, T and *Saccharomyces boulardii* CNCM I-745).

1 additional day of diarrhea (mean 4.4 + 2 days) compared to those receiving *S. boulardii* (mean 3.3 + 1.6 days, with a significant reduction in duration of diarrhea (SMD = -1.1 days, 95%

CI -1.3, -0.8, $P < .05$).^[15] In addition, those receiving *S. boulardii* had shorter lengths-of-stay for inpatients (8 RCT, SMD = -0.8 days, 95% CI -1.3, -0.3).^[15] Collinson et al also found a

Table 2
Primary outcome, sensitivity analyses, and secondary outcomes.

	<i>Saccharomyces boulardii</i> CNCM I-745	<i>Bacillus clausii</i> O/C, SIN, N/R, T	P value
Primary outcome			
Adjusted mean duration diarrhea during study, hrs (95% CI), ITT*	(n = 157) 64.61 (56.45, 72.76)	(n = 158) 77.98 (69.86, 86.11)	.04
Sensitivity analyses			
Total mean duration of diarrhea, hrs (95% CI)†	112.2 (103.8, 120.7)	131.4 (123.0, 139.9)	.05
Adjusted mean duration diarrhea during study, hrs (95% CI), APP*	(n = 133) 65.58 (57.65, 73.51)	(n = 130) 80.08 (72.06, 88.09)	.04
Mean ± SD duration of diarrhea by etiology:‡			
Bacterial	88.6 ± 64.7 (n = 19)	139.9 ± 47.6 (n = 10)	.04
Viral	54.9 ± 26.6 (n = 20)	59.9 ± 34.6 (n = 21)	.60
Secondary outcomes			
Frequency of stools/day on Day 6 (mean ± SD)	1.0 ± 1.2	1.1 ± 1.4	.50
Number (%) with loose stools on Day 6	34 (21.7)	36 (23.1)	.95
Number (%) cured by Day 6	119 (76.3)	113 (71.5)	.38
Time-to first formed stool, mean hours (95% CI)	71.4 (62.0, 82.2)	76.5 (71.4, 94.0)	.11
Recurrence of diarrhea before Day 12, number (%)	3 (1.9)	1 (0.6)	.37
Compliance, % (>80% doses taken)	98.5 ± 6.5	99.3 ± 3.6	.22

APP = as per protocol analysis, CI = confidence interval, hrs = hours, ITT = intent to treat analysis, SD = standard deviation.

* Adjusted for study site, age (years) and days of diarrhea prior to enrollment.

† Total duration of diarrhea from initial onset to cessation during study, assessed by parents.

‡ Bacterial (Salmonella, Shigella, Campylobacter) or viral etiologies (rotavirus, adenovirus).

significant reduction in diarrhea (-1 day) in his meta-analysis of 11 RCTs with *S. boulardii*.^[32] No meta-analyses of only community-acquired PAGE and probiotics were found in the literature. Ianiro et al pooled 6 RCTs with *B. clausii* and found a lesser degree of reduction in duration of diarrhea compared to placebo (SMD = -0.4 days, 95% CI = -0.69 to -0.07, $P = .02$).^[16] These data show the degree of reduction in diarrhea duration between treatment groups is similar in direct probiotic to probiotic studies to those studies which compared probiotics to a placebo control. The efficacy of *S. boulardii* over *B. clausii* is supported even when placebo controls are not used. Most of the trials testing either of these 2 probiotics have not been based on the age or weight of the children. Another limitation is that the assessment of outcomes was not blinded throughout the study, due to the different formulations of the 2 probiotics (sachets or vial). However, at the time of study treatment allocation, the study medication was given out blinded due to identical study packaging.

The generalizability of the study results may not be applicable for children with more severe PAGE or if hospitalized since the study children had mild-moderate PAGE and were seen as outpatients.

Safety data indicated both probiotic types were well-tolerated, which has been confirmed in other studies of *S. boulardii* CNCM I-745,^[6,17] and *B. clausii*^[16,33] but rare cases of septicemia has been reported for both probiotics.^[34,35]

Recommendations for future studies include the need to use standard definitions and standard, common PAGE outcomes so the results of different trials can be compared. It would be useful to collect cost-data for the different probiotic treatments to document cost-savings to healthcare administrations and practitioners.

5. Conclusions

In this randomized direct comparison study, *S. boulardii* CNCM I-745 was the more efficacious in reducing the duration of PAGE. Reduction in the duration of diarrhea is an important outcome for both parent/caregivers and their physicians and eases the burden of health care.

Author contributions

We would like to thank Dr Leylen Colmegna, from LAT Research CRO, for their local management of the study. **Conceptualization:** Jaime Altcheh, Ana Ceballos, Ulises D'Andrea,

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Corrections

Some minor formatting and capitalization changes have been made that do not effect meanings. The symbol in "...bacterial etiologies (88.6 + 64.7 hours...)" has been corrected to +/- . In table 2, the P value for "Recurrence of diarrhea before Day 12, number (%)" has been corrected to .37 from 037.

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