Bacillus clausii in the treatment of acute community-acquired diarrhoea among Latin American children (cadiLAc)

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INTRODUCTION

- Acute community-acquired diarrhoea is a principal cause of childhood mortality in developing countries.[1]
- Noroviruses are recognised as a mejor cause of acute gastroenteritis with a prevalence rate of 15% among Latin American (LATAM) communities.[2]
- Oral rehydration therapy (ORT) is the optimal treatment to minimise the risk of dehydration.[3]
- ORT does not decrease diarrhoea duration or stool volume thus active treatment with probiotics as adjunct is recommended.[3]
- *Bacillus clausii (B. clausii)* is a commercially available oral preparation containing four bacterial strains: O/C, SIN, N/R and T.[3]

OBJECTIVE

- The objective of this study was to evaluate the effectiveness, acceptability and safety of *B. clausii* as an adjunct to ORT in the treatment of acute community-acquired diarrhoea in Latin American children and without a positive norovirus test.

METHODS

Multicentre · Phase IV · Open-label · Latin American (Argentina, Brazil, Colombia, Guatemala, México and Peru) · Prospective

- The study was approved by the research ethics committees at each study site (NCT02169817).

Inclusion criteria	Exclusion criteria	
Age: 6 months - 5 years	Blood, pus or mucus in stools	Required hospitalisation
Non-severe acute community-acquired diarrhoea	Severe dehydration per WHO criteria	Treated with antibiotics, probiotics or prebiotics within 2 weeks*
Diagnosis ≤ 48h*	Untreatable vomiting	Treated with anti-diarrheal agents within 48h*

* Prior to study entry.

Study design

- **Visit 1, Day 1**: Data collection; Norovirus test
- **Treatment**: Eligible children; *B. clausii* TWICE daily/5 days + ORT low osmolarity formulation of 245 mmol/L
- **Visit 2, Day 6-10**: Data collection

ORT, Oral Rehydration Therapy.

OUTCOMES

Primary efficacy	Sencondary efficacy**	Safety & acceptability
Mean duration of diarrhoea (in hours) between the first B. clausii intake and the last appearance of a loose (or watery) stool*	1. Mean number of stools per day 2. Stool consistency 3. Mean number of vomiting episodes per day 4. Frequency of norovirus infection	Assessment of safety and tolerability of B. clausii therapy was based on: 1. Medical examination 2. Legal guardians´ assessment of children´s overall acceptability of the therapy and children´s overall general condition

* Defined by two following and consecutive normal stools.
** All evaluated between Day 1-5 of the study.

Statistics

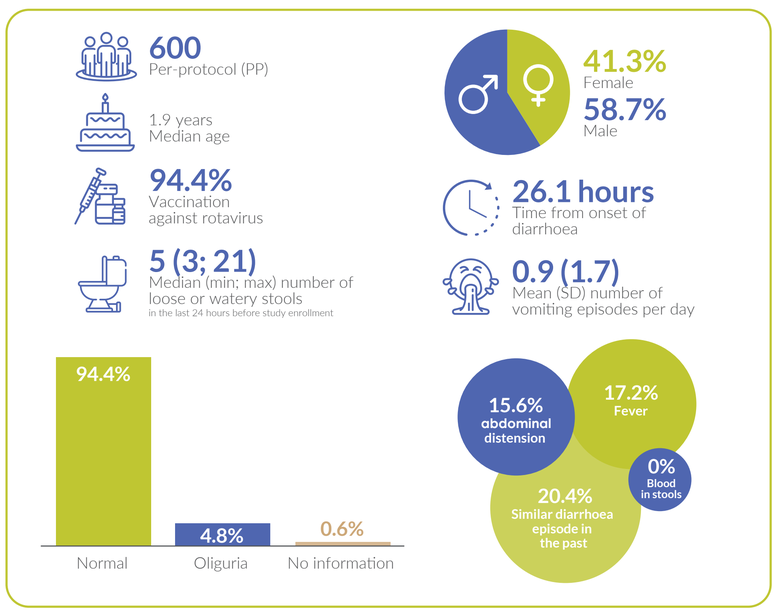
Intention-to-treat (IIT): Demographic and baseline characteristics and safety analysis were described for the intention-to-treat (ITT) population (all patients with signed informed consent).

Per-protocol (PP): Primary efficacy analyses were performed for the per-protocol (PP) population (all patients without protocol deviations).

- Data analysis was descriptive; statistical methods included variance analyses with repeated measures (CI: 95%, two-sided p value ≤0.005) and Student's † test.

RESULTS

- A total of 627 children were enrolled in the study (intention-to-treat, ITT).



% calculated as n/N, unless otherwise specified. ITT, intention-to-treat; SD, standard deviation.
* Defined in hours as (date and time of baseline visit - date and time of onset of diarrhoea) / 3600.

Efficacy results

In the PP population: **82.9 ± 40.1 hours** Mean (SD) duration of diarrhoea

During the **5-day treatment** period, diarrhoea was resolved in **52%** of children with a mean duration of diarrhoea of **48.7 hours.**

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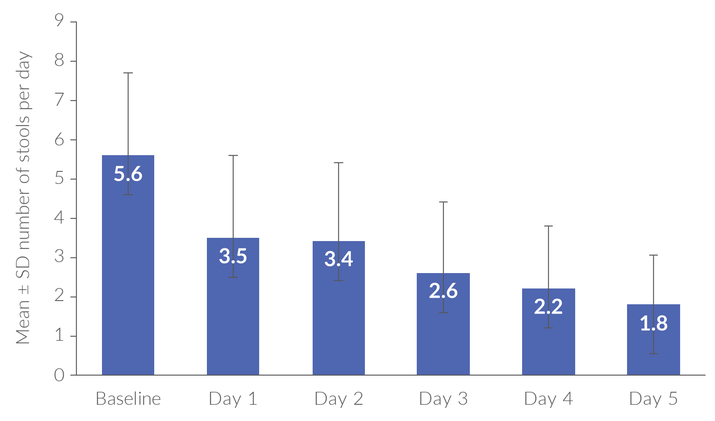
- There was a significant decrease (p<0.001) in the mean ± SD number of stools per day from baseline (5.6 ± 2.2 stools/day) to Day 5 of treatment (1.8 ± 1.5 stools/day), **Figure 1.**

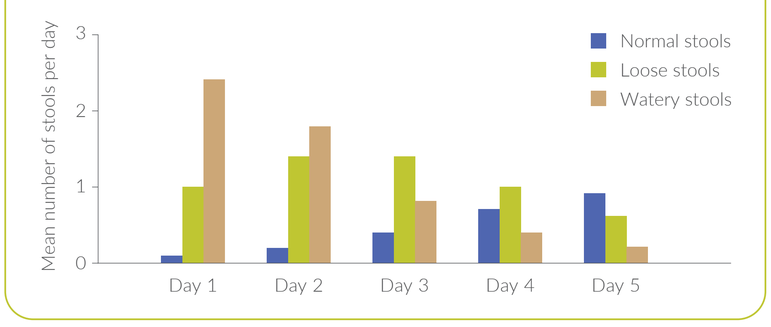
Figure 1: Mean ± Standard Deviation (SD) number of Stools Per Day (PP population).



At baseline, the total number of stools per day corresponds to the maximum number of stools in the last 24 hours before study entry.
PP, per-protocol.

- Stool consistency improved over time with a gradual decrease of watery stools from 2.4 ± 2.4 occurrence per day at baseline down to 0.2 ± 1.0 at Day 5, **Figure 2.**

Figure 2: Mean number of normal, loose or watery stools per day (PP population).



PP, per-protocol.

Norovirus tested in 547 samples

- **12.2%** Positive **vs** **87.8%** Negative

85 ± 37.7 hours Mean (SD) duration of diarrhoea

82.6 ± 40.9 hours Mean (SD) duration of diarrhoea

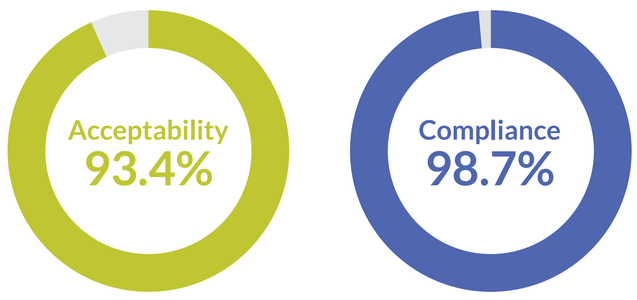
NO SIGNIFICANT DIFFERENCE (p=0.646)

Safety and tolerability results

- Overall, therapy with *B. clausii* was well-tolerated, without causing treatment-related serious adverse events.

2.6% Pyrexia · **1.3%** Cough · **1.1%** Rhinorrhoea

- Children's acceptability of the study therapy was rated as good to excellent and high compliance rate was noted.



SUMMARY AND CONCLUSIONS

- This was the first large-scale study in Latin America investigating the real-world effectiveness, acceptability and safety of *B. clausii* in the treatment of children with acute community-acquired diarrhoea.
- In addition, a high compliance rate to *B. clausii* therapy was noted.
- There was no difference in diarrhoea duration between norovirus positive and negative samples.
- A limitation of this study was the absence of a comparator arm in the observational setting.
- The results of this study support the role of B. clausii as adjuvant to ORT in the management of acute childhood diarrhoea.
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