CLINICAL EVIDENCE SUMMARY BOOKLET

Anti-regurgitation formula with carob bean gum, prebiotics and postbiotics

For healthcare professionals only, not for distribution to the general public.

Anti-regurgitation (AR) formula is a Food for Special Medical Purposes (FSMPs) for use under medical supervision, after full consideration of feeding options available including breastfeeding.

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INTRODUCTION

This booklet presents the recent clinical studies and summarizes the latest clinical evidence supporting the role of the anti-regurgitation (AR) formula containing carob bean gum (CBG)*, prebiotics scGOS/lcFOS (9:1) and postbiotics in the dietary management of infant reflux and regurgitation.

Supported by an extensive clinical trial program in >3000 infants with regurgitation:

- 2 randomized controlled trials (RCTs)[1,2]
- 2 real world evidence studies[3,4]

All 4 studies** showed that the **AR formula is clinically proven to reduce regurgitation frequency and severity**[1-4]

ADDITIONAL OUTCOMES:

SAFETY, TOLERANCE AND GROWTH	GASTROINTESTINAL (GI) SYMPTOMS	STOOLS	QUALITY OF LIFE
■ Safe and well tolerated[1,2,3,4] ■ Supporting adequate growth[1,2,3,4]	■ Significant improvement of several GI symptoms such as crying and fussiness within one week with further improvement over time[1] ■ Decreased frequency and duration of crying[3,4] ■ Decreased gassiness and fussiness[3] ■ Improvement of overall GI burden over time[1,2] ■ Greater improvement of overall GI burden in infants with more severe GI burden at baseline[1]	■ Low incidence of diarrhea and flatulence constipation[1,2] ■ High parental satisfaction with stool consistency[4]	■ High parental satisfaction with the formula[2,4], overall wellbeing of the infant[2,4] and sleep quality[3,4] ■ Improvement of infant agitation and parental anxiety[3]

*CBG, a dietary fibre and thickener, is also known as locust bean gum (LBG). In this booklet we refer to CBG.

**The test formulas of the Bellaiche 2021, Salvatore 2024, and Bellaiche 2023 studies contained CBG, prebiotics and postbiotics. The Tounian 2020 study contained CBG and postbiotics only.

1. Bellaiche M et al. 2021, ** AR formula containing CBG, prebiotics and postbiotics

2. Salvatore S et al. 2023, ** AR formula containing CBG, prebiotics and postbiotics

3. Tounian P et al. 2020, ** AR formula containing CBG and postbiotics

4. Bellaiche M et al. 2023, ** AR formula containing CBG, prebiotics and postbiotics

SUMMARY OF THE FOUR STUDIES

REFERENCE	STUDY DESIGN & POPULATION	STUDY GROUPS	STUDY PERIOD	OUTCOMES*
Bellaiche, M et al. Journal of Pediatric Gastroenterology and Nutrition. 2021;73(5):579. **1.**	■ RCT ■ Infants 3-13 weeks old with diagnosed regurgitation	■ Test: **AR formula containing CBG, prebiotics and postbiotics** (n=92) ■ Control: AR formula containing CBG and postbiotics (n=90)	4 weeks, optional 4 weeks extension	■ Both test and control AR formulas were well-tolerated and safe in infants with regurgitation. ■ Significant reduction of regurgitation within the first week for both test and control AR formulas (p<0.001). ■ Significant improvement of overall GI burden (p<0.001) and most other GI symptoms (e.g. stooling, crying, gassiness and fussiness) with both test and control AR formulas within the first week with further improvement over time. ■ Post-hoc analyses show greater improvement of GI burden in infants with more severe symptoms who received the test AR formula containing CBG, prebiotics and postbiotics.
Salvatore S et al. Nutrients. 2024; 16: 899. **2.**	■ RCT ■ Infants enrolled at 3-9 weeks old with diagnosed regurgitation	■ Test: **AR formula containing CBG, prebiotics and postbiotics** (n=51) ■ Control: Unthickened formula with prebiotics and postbiotics (n=52)	8 to 14 weeks	■ Both study products were well-tolerated and safe in infants with regurgitation. ■ The stool consistency of infants consuming the test AR formula containing CBG was not leading to more loose/watery stools as compared to the stool consistency of infants consuming the unthickened control formula. ■ Regurgitation frequency was significantly lower in the test AR formula containing CBG versus the unthickened control formula group at all post-baseline points (p≤0.028). ■ Improvement of overall GI burden over time in both study groups.
Tounian, P et al. Pediatric Gastroenterology, Hepatology & Nutrition. 2020;23(6):511. **3.**	■ Observational study ■ Infants aged on average 9±4 weeks with moderate to severe regurgitation (according to parents)	■ AR formula containing CBG and postbiotics (n=2604)	1 month	■ Regurgitation frequency and volume decreased significantly (p<0.001). ■ Stool frequency was higher, and stools were softer after 1 month (p<0.001). ■ Crying frequency and duration significantly decreased (p<0.001). ■ All other quality of life indicators of sleep quality, agitation, and parental anxiety levels improved significantly over the study period.
Bellaiche M et al. Pediatr Gastroenterol Hepatol Nutr. 2023 Sep;26(5): 249-265. **4.**	■ Observational study ■ Infants aged on average 1.9 months with diagnosed regurgitation	■ **AR formula containing CBG, prebiotics and postbiotics** (n=190)	3 months	■ Stool frequency and consistency remained in the normal physiological range. ■ Regurgitation severity significantly decreased (p<0.001). ■ Colic significantly reduced after 1 and 3 months (p<0.001). ■ Crying decreased during the first month. ■ Parental satisfaction with stool consistency, formula acceptability, infant wellbeing, and sleep quality was high (all >85%). ■ Over 3 months, infants showed adequate growth.

LEGEND

- **AR formula containing CBG, prebiotics scGOS/lcFOS (9:1) and postbiotics derived from the Lactofidus™ fermentation process**
- AR formula containing CBG and postbiotics derived from the Lactofidus™ fermentation process
- Unthickened formula with prebiotics scGOS/lcFOS (9:1) and postbiotics derived from the Lactofidus™ fermentation process

*Includes primary, secondary and exploratory study outcomes

1. SAFETY AND TOLERANCE OF A NOVEL ANTI-REGURGITATION FORMULA: A DOUBLE-BLIND, RANDOMIZED, CONTROLLED TRIAL

Bellaiche, M et al. Journal of Pediatric Gastroenterology and Nutrition. 2021;73(5):579.

OBJECTIVES

The anti-regurgitation (AR) formula containing carob bean gum (CBG), prebiotics and postbiotics has been designed to support gut health and improve gastrointestinal (GI) symptoms beyond regurgitation. This study assessed the tolerance and safety of this AR formula.

Both AR formulas containing CBG improved regurgitation and most GI symptoms (e.g. stooling, crying, fussiness) within one week of intervention

METHODS

This was a 4-week double-blind, randomized, controlled trial with a 4-week extension in formula-fed infants with regurgitation. The test AR formula contained CBG (0.4g/100ml), prebiotics (scGOS/lcFOS; 9:1; 0.4g/100ml) and postbiotics derived from Lactofidus™ fermentation process. The control AR formula contained CBG (0.4g/100ml) with postbiotics and has a history of safe use. The primary outcome was the Infant Gastrointestinal Symptom Questionnaire (IGSQ) sum score including stooling, spitting-up/vomiting, crying, fussiness and flatulence.

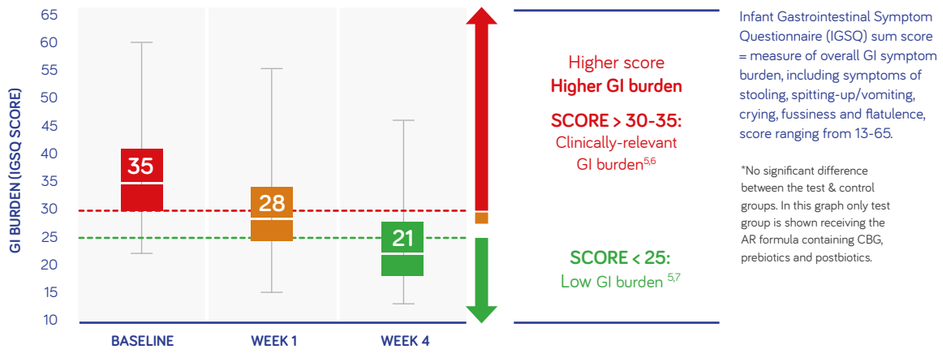
RESULTS

All 182 infants screened were enrolled in the study. The primary analysis showed the equivalence of the IGSQ sum scores at Week 4 between groups. IGSQ sum scores improved significantly within 1 week (Mixed Model Repeated Measurement [MMRM], p<0.001). Post-hoc analyses showed a bigger improvement of the IGSQ score in the test (n=38) versus control (n=44) group (MMRM, p=0.008) in infants with more severe GI symptoms (IGSQ score ≥35). Stool characteristics were comparable between groups. Growth related z-scores were in line with the WHO child growth standards and both groups showed improvement of regurgitation. Adverse events did not show any safety concerns.

CONCLUSIONS

The test AR formula containing CBG, prebiotics and postbiotics is well-tolerated, safe and supports adequate growth during the intervention. Post-hoc analyses suggest that the AR formula containing CBG, prebiotics and postbiotics results in more improvement of GI symptom burden in infants with more severe symptoms.

Improvement of overall GI burden with AR formula containing CBG, prebiotics and postbiotics over time*



5. Riley AW et al. Clin Pediatr (Phila) 2015;54(12):1167-74. **6.** Pados BF & Basler A. J Pediatr Nurs 2020;53:1-5. **7.** Storm HM et al. Glob Pediatr Health 2019;6:1- 10

STUDY GROUPS

Test: **AR formula containing CBG, prebiotics scGOS/lcFOS (9:1) and postbiotics derived from the Lactofidus™ fermentation process**

Control: **AR formula containing CBG and postbiotics derived from the Lactofidus™ fermentation process**

2. TOLERANCE AND SAFETY OF AN ANTI-REGURGITATION FORMULA CONTAINING CAROB BEAN GUM, PRE- AND POSTBIOTICS: AN INTERNATIONAL MULTICENTER PROSPECTIVE RANDOMIZED CONTROLLED TRIAL IN INFANTS WITH REGURGITATION

Salvatore S et al. Nutrients. 2024; 16: 899.

OBJECTIVES

The primary study aim was to assess non-inferiority of stool consistency (i.e. not more loose or watery stools) in infants with regurgitation fed an anti-regurgitation (AR) formula containing carob bean gum (CBG), prebiotics and postbiotics versus an unthickened control formula after 8 weeks intervention.

Infants fed the AR formula containing CBG, prebiotics and postbiotics showed a significantly lower regurgitation frequency as compared to the unthickened control formula

METHODS

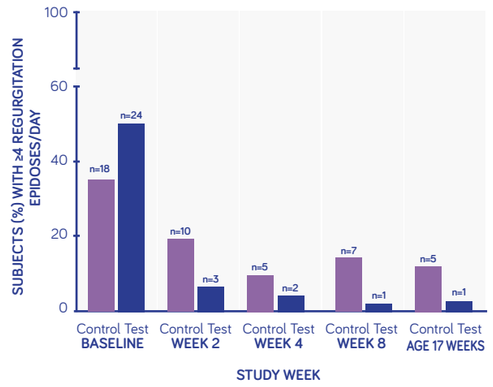
This multicenter prospective RCT enrolled full-term infants with regurgitation. Participants were randomized to the test AR formula containing CBG (0.4g/100ml), prebiotics (scGOS/lcFOS; 9:1; 0.4g/100ml) and postbiotics derived from Lactofidus™ fermentation process, or the unthickened control formula containing prebiotics (scGOS/lcFOS; 9-1; 0.8g/100ml) and postbiotics. Study outcomes were stool consistency and frequency, Infant Gastrointestinal Symptom Questionnaire (IGSQ) score, (S)AEs, growth, and regurgitation severity. The study was approved by IRBs and registered at ClinicalTrials.gov (NCT04042454). A linear Mixed Model Repeated Measurement was used for the primary analysis.

RESULTS

103 infants (3-9 weeks old) were enrolled; 93 completed the study. The test group did not have more loose or watery stools than the control group (non-inferiority testing), and there were more loose and fewer formed stools in the control versus test group. Both groups grew adequately. The (S)AE incidence did not indicate concerns and was comparable between groups. The incidence of diarrhoea (3.9% in test; 3.8% in control) and flatulence (2.0% in test; 1.9% in control) was low. No constipation was reported. The IGSQ sum score decreased comparably in both groups. Regurgitation frequency was significantly lower in the test versus control group at all post-baseline timepoints (p≤0.028). Within 2 weeks the number of subjects with ≥4 regurgitations/day decreased by 86.4% in the test versus 44.5% in the control group.

Decreased regurgitation severity over time

Within 2 weeks the number of subjects with ≥4 regurgitations/day decreased by 86.4% in the test versus 44.5% in the control group.



CONCLUSIONS

The test AR formula containing CBG, prebiotics and postbiotics did not lead to more loose or watery stools than the unthickened control formula. Both products were well-tolerated and safe. The AR formula containing CBG, prebiotics and postbiotics showed a significantly lower regurgitation frequency as compared to the unthickened control formula.

STUDY GROUPS

Test: **AR formula containing CBG, prebiotics scGOS/lcFOS (9:1) and postbiotics derived from the Lactofidus™ fermentation process**

Control: **Unthickened formula with prebiotics scGOS/lcFOS (9:1) and postbiotics derived from the Lactofidus™ fermentation process**

3. EFFECTIVENESS AND TOLERANCE OF A CAROB BEAN GUM-THICKENED FORMULA: A REAL-LIFE STUDY

Tounian, P et al. Pediatric Gastroenterology, Hepatology & Nutrition. 2020;23(6):511.

OBJECTIVES

This study evaluated the tolerance and effectiveness of the anti-regurgitation (AR) formula containing carob bean gum (CBG) and postbiotics in infants with regurgitation.

Large real-life study in 2604 infants with regurgitation showed decreased regurgitation, in frequency and volume, after using the AR formula containing CBG and postbiotics

METHODS

We conducted an observational study among infants with moderate to severe regurgitation, according to parents, who received the AR formula containing CBG and postbiotics derived from the Lactofidus™ fermentation process for one month. Tolerance and effectiveness were assessed by the evaluation of gastrointestinal (GI) symptoms and quality of life indicators.

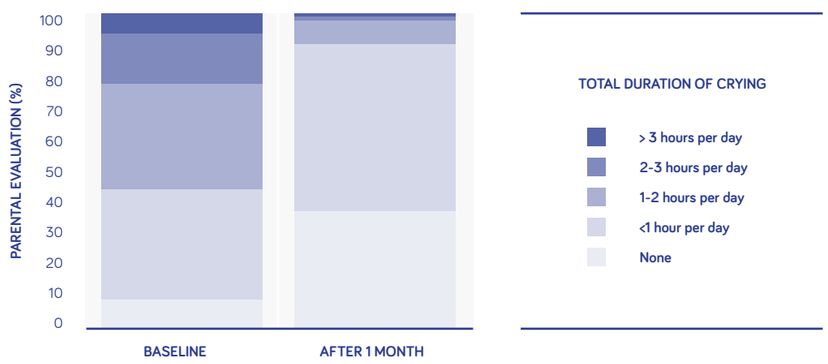
RESULTS

In total 2604 infants aged on average 9.3 ± 4.3 weeks were enrolled in this study.
A significant decrease in regurgitation frequency and estimated volume was observed ($p<0.001$). In nearly half (48%) of the infants the regurgitation episodes resolved completely after one month of the AR formula feeding. Additionally, increased stool frequency and softened stool consistency ($p<0.001$) were observed after one month. These parameters remained within the physiological range. Lastly, significant improvements in crying duration, episodes of gas ($p<0.001$) and quality of life parameters were reported.

CONCLUSIONS

This study showed that the AR formula containing CBG and postbiotics was effective for the dietary management of infant regurgitation, was well tolerated and improved quality of life indicators. After a month of the AR formula feeding, a softening effect on stool consistency and an increased in stool frequency was demonstrated. These changes remained within the normal physiological range.

Decreased duration of crying after 1 month



STUDY GROUP
AR formula containing CBG and postbiotics derived from the Lactofidus™ fermentation process

4. DIGESTIVE TOLERANCE AND SAFETY OF AN ANTI-REGURGITATION FORMULA CONTAINING CAROB BEAN GUM, PREBIOTICS AND POSTBIOTICS: A REAL-WORLD STUDY

Bellaiche M et al. Pediatr Gastroenterol Hepatol Nutr. 2023 Sep;26(5):249-265.

OBJECTIVES

The primary study aim was to assess the safety, tolerance and effectiveness of an anti-regurgitation (AR) formula containing carob bean gum (CBG), prebiotics and postbiotics.

Consumption of the AR formula containing CBG, prebiotics and postbiotics resulted in a significant reduction of regurgitation severity, infant crying, and improvement of family centered outcomes

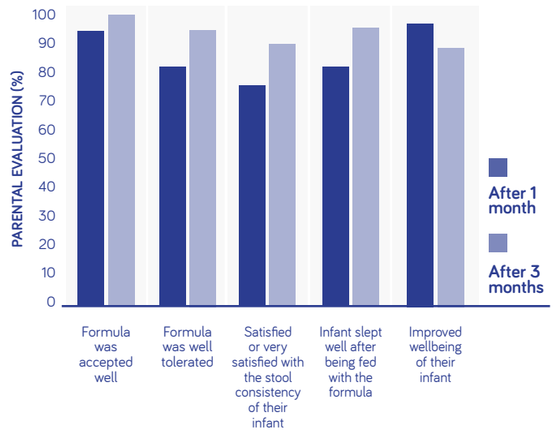
METHODS

This multicenter 3-month observational study involved full-term infants with regurgitation requiring an AR formula prescription according to usual clinical practice. The AR formula contained CBG (0.4g/100ml), prebiotics (scGOS/lcFOS; 9:1; 0.4g/100ml) and postbiotics derived from Lactofidus™ fermentation process. Study outcomes were stool consistency and frequency, prevalence of colic, constipation and diarrhea, regurgitation severity and growth characteristics, evaluated after 1 and 3 months of product use (M1, M3). Parental assessments of crying, infant wellbeing and sleep quality, and parent satisfaction with stool consistency were also evaluated.

RESULTS

Overall, 190 infants (average age: 1.9 months) were included. At M3, stool frequency and consistency remained in the normal physiological range, with 82.7% of infants passing 1 or 2 stools per day and 90.4% passing loose or formed stools. There was no significant increase in the number of infants with diarrhea versus baseline. Compared to baseline, a significant lower number of infants experienced constipation at M1 ($p=0.001$), and colic at M1 and M3 ($p<0.001$). Regurgitation severity significantly decreased for 83.4% of infants at M1 and 92.6% of infants at M3 versus baseline ($p<0.001$). Infants crying for less than 1 hour per 24-hour significantly increased from 29.3% at baseline to 74.9% at M1 and 88.9% at M3. At M3, scores for parental assessments outcomes were all high (all > 85%). Over 3 months, infants showed adequate growth and the low incidence of (Serious) Adverse Events indicated no safety concern.

Acceptability of the AR formula and impact on infant quality of life and wellbeing, as reported by the parents



CONCLUSIONS

The AR formula containing CBG, prebiotics and postbiotics was well tolerated and appeared to provide an effective strategy for managing the complete range of issues associated with infant regurgitation and gastrointestinal (GI) discomfort in a real-world study setting. Moreover, parent satisfaction and infant acceptability of the formula were high, and assessments of crying and infant wellbeing suggested that the formula helped to address the broader family-centered issues associated with functional gastrointestinal disorders and GI discomfort.

STUDY GROUP
AR formula containing CBG, prebiotics scGOS/lcFOS (9:1) and postbiotics derived from the Lactofidus™ fermentation process

At Nutricia, we believe in the power of nutrition to make a positive and measurable difference to health. Every day we are inspired by our purpose: to pioneer nutritional discoveries that help people of every age live longer, healthier lives.

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