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Original Article

Digestive Tolerance and Safety of an Anti-Regurgitation Formula Containing Locust Bean Gum, Prebiotics and Postbiotics: A Real-World Study

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ABSTRACT

Purpose: Infant regurgitation is associated with other functional gastrointestinal disorders and signs and symptoms that have a major impact on the quality of life of infants and their families. This study evaluated the safety, tolerance, and real-world effectiveness of an anti-regurgitation formula containing locust bean gum (LBG), prebiotics, and postbiotics to alleviate digestive symptoms beyond regurgitation.
Methods: This 3-month study involved infants with regurgitation requiring the prescription of an anti-regurgitation formula according to usual clinical practice. Outcomes included evaluation of the evolution of stool consistency and frequency; occurrence of colic, constipation, and diarrhea; and assessment of regurgitation severity. Infant crying, parental assessment of infant well-being, and parental satisfaction with the stool consistency were also evaluated.
Results: In total, 190 infants (average age: 1.9±1.1 months) were included. After three months, stool frequency and consistency remained within the normal physiological range, with 82.7% of infants passing one or two stools per day and 90.4% passing loose or formed stools. There was no significant increase in the number of infants with diarrhea, whereas a decrease was observed in the number of infants with constipation after 1 month (p=0.001) and with colic after both 1 and 3 months (p<0.001). Regurgitation severity and crying decreased and parental satisfaction with stool consistency, formula acceptability, infant well-being, and sleep quality increased. Monitoring of adverse events did not reveal any safety concerns.
Conclusion: Formulas containing LBG, prebiotics, and postbiotics were well tolerated and provided an effective strategy for managing infant regurgitation and gastrointestinal discomfort.

Keywords: Locust bean gum; Quality of life; Infant well-being; Nutritional support; Colic; Diarrhea; Crying; Defecation; Digestive tolerance; Infant formula; Constipation; Gastroesophageal reflux; Infant health

Funding

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Conflict of Interest

Raish Oozeer and Emilie Rocher are employees of Danone Nutricia Research. Marc Bellaiche, Patrick Tounian, and Yvan Vandenplas received fees for participating in the scientific committee of the study.

INTRODUCTION

Regurgitation is very common in infancy, affecting up to 30% of infants worldwide [1]. It is often associated with other functional gastrointestinal disorders (FGIDs), such as colic and constipation, and gastrointestinal (GI) signs and symptoms, such as gassiness, hard stools, straining, crying, and sleeping problems [2,3]. These signs and symptoms can lead to significant infant distress and are a frequent cause of concern for parents and caregivers, resulting in parental stress, anxiety, frustration, lack of sleep, work absenteeism, and poor quality of life (QoL) for families [3,4]. FGIDs in infancy, particularly colic and constipation, have also been associated with long-term health issues, such as GI disorders (symptoms of GI reflux and recurrent abdominal pain), sleep disorders, behavioral problems (aggressiveness, fussiness, and feelings of supremacy), allergic diseases (asthmatic bronchitis, allergic rhinitis, conjunctivitis, atopic eczema, and food allergies), and migraines during childhood [5-7].

Therefore, FGIDs and GI discomfort are common reasons for pediatric consultation, with repeated medical visits, prescriptions of largely ineffective pharmacological treatments, and the purchase of over-the-counter remedies, resulting in a significant financial burden for families and healthcare systems [4,8-10]. Moreover, some of these medications may be associated with adverse effects, most commonly GI dysbiosis and small bowel bacterial overgrowth, associated with the use of proton pump inhibitors [4,10].

To address the global issues associated with FGIDs, early management with parental education, reassurance, and nutritional advice (feeding technique, feed volume and frequency, and the importance of avoiding overfeeding) are now the recommended first-line strategies, rather than medical interventions [8,10-12]. For non-exclusively breastfed infants with regurgitation, expert guidelines recommend the use of thickened formulas as a first-line nutritional management option to reduce the frequency and severity of symptoms [12]. These anti-regurgitation (AR) formulas may contain a range of thickening agents to increase viscosity, including starch-based thickeners (e.g., corn or rice starch) or soluble fiber-based thickeners, such as pectin and locust bean gum (LBG) [10,13]. Thus, LBG is a safe and effective thickening agent [10,14-17]. In addition, in vitro studies have indicated that LBG has a lower caloric value and higher viscosity than starch-based thickeners, because it remains unaffected by pH and is resistant to digestion by salivary amylases [10,13].

For healthy formula-fed infants, studies have indicated that formulas containing a combination of a specific mixture of prebiotics (short-chain galacto-oligosaccharides and long-chain fructo-oligosaccharides in a ratio of 9:1; scGOS/lcFOS) and postbiotics (bioactive compounds derived from the Lactofidus™, Danone Nutricia Research, in which the food-grade microorganisms *Bifidobacterium breve* C50 and *Streptococcus thermophilus* 065 are used to ferment the milk matrix) may have a positive impact on microbiota composition, gut health, stool characteristics, and the immune system [18-22].

A new AR formula containing LBG, prebiotics (scGOS/lcFOS, 9:1), and postbiotics (derived from the Lactofidus™ process) was recently developed to help manage the associated GI symptoms in infants with regurgitation. The tolerance and safety of this new formula have been demonstrated in an 8-week double-blind randomized controlled trial (RCT) involving infants with regurgitation [17]; however, its long-term impact has not yet been evaluated in real-world practice. Therefore, the current study aimed to assess the digestive tolerance and safety of this new formula in infants with regurgitation in a real-world setting over a longer

3-month period as well as to evaluate a broader range of parameters related to infant growth, QoL, well-being, parental satisfaction, and infant acceptability of the new formula.

MATERIALS AND METHODS

Study design and setting

This multicenter observational prospective study was conducted by community pediatricians in France between November 2019 and January 2021. The study involved an inclusion visit (baseline) and two follow-up visits at months 1 (M1; between 18 and 44 days after inclusion) and 3 (M3; between 70 and 120 days after inclusion). These visits were part of the routine follow-up of the patient by a pediatrician who was normally responsible for their care. All infants were managed according to the usual practice of the pediatrician in cases of uncomplicated infantile regurgitation, and no additional invasive or specific examinations were performed. All data were collected using a questionnaire (provided as supplementary information, Appendix 1) administered at each study visit and completed by a pediatrician based on parental recall.

The study was conducted in accordance with good clinical practice guidelines and the study protocol was approved by the Institutional Review Board (Comité de Protection des Personnes SUD MEDITERRANNEE IV: CPP 190704). Personal data processing was approved by the French Data Protection Agency (Commission Nationale de l'Informatique et des Libertés). All parents or guardians provided oral informed consent before inclusion after being informed about the study.

Study population

Pediatricians were invited by the study sponsor to participate in the study, and were asked to recruit the first eight infants presenting with uncomplicated infantile regurgitation requiring parental reassurance, nutritional advice, and prescription of a thickened AR formula. Pediatricians were free to prescribe any commercially available AR formula as per their usual clinical practice and in accordance with current management guidelines [11,12], and only infants who were prescribed the study formula (Gallia AR, Danone, Nutricia) and met all other eligibility criteria (**Supplementary Table 1**) were enrolled in the study.

Study procedure

Pediatricians collected data on the demographic and anthropometric characteristics of the infants and their feeding habits. Anthropometric data were used to calculate individual sex-adjusted weight-for-age, weight-for-length, length-for-age, and head circumference-for-age z scores based on WHO standards [23]. Data on stool frequency, stool consistency according to the Brussels Infant and Toddler Stool Scale [24,25], occurrence of digestive symptoms (diarrhea, constipation, and infantile colic), regurgitation severity according to adapted Vandenplas scale scores [14,26] and crying, all based on parental recall from the previous 24 hours, were also collected.

Subsequently, the pediatrician prescribed the study formula: a cow's milk-based, nutritionally complete infant formula complying with European regulations and containing the thickener LBG (0.4 g/100 mL), prebiotics scGOS and lcFOS (0.4 g/100 mL, 9:1 ratio), and postbiotics derived from Lactofidus™ fermentation (26% fermented infant formula). Details of the main ingredients in the formula have been published previously [17].

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At the follow-up visits (M1 and M3), pediatricians again collected data on infant characteristics, stool frequency and consistency, digestive symptoms, regurgitation severity, and crying, and gathered information on parental satisfaction with stool consistency and their perceptions of how the well-being of the infant had changed since the previous visit. Parents' perceptions of the acceptability of the formula, apparent ease of digestion, and sleep quality after feeding were also assessed. The tolerance and safety of the formula were evaluated by reporting adverse events (AEs) and/or respiratory infections that occurred from the start of the study.

Outcome measures

The primary outcome measure was the digestive tolerance of the formula, assessed by evaluating the stool frequency and consistency, and the evolution of digestive symptoms (diarrhea, constipation, and colic) between visits. Secondary outcome measures were assessments of regurgitation severity, growth characteristics, and the safety and acceptability of the formula, as well as evaluations of infant crying and well-being, and parent satisfaction with stool consistency during the study period.

Study size

An initial sample size of 320 infants was calculated using the PASS 15 Power Analysis and Sample Size Software (2017). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass., considering the results of a previous study [15] and an estimated dropout rate of 15%. However, as the impact of the coronavirus disease (COVID-19) pandemic slowed recruitment, enrollment was halted after 190 infants were included.

Statistical methods

All analyses were planned to be conducted on the main study population of eligible infants for whom data for the primary outcome measure were available at baseline, and at least one of the follow-up visits was performed within the specified time windows. However, due to the impact of the COVID-19 pandemic resulting in delays in medical visits, analyses of the primary and secondary outcome measures were conducted on a wider study population (digestive tolerance population, N=157), including infants for whom data were collected outside of the defined visit time windows. In addition, analyses of AEs, respiratory infections, and growth parameters were based on data from a safety population (N=183), including all infants who consumed the study product at least once and attended at least one follow-up visit.

Descriptive data were expressed as mean and standard deviation (SD), median, and first and third quartile (Q_1-Q_3) for continuous variables, and as frequency and percentage for categorical variables. Changes from baseline at M1 and M3 were analyzed using a paired *t*-test or Wilcoxon signed-rank test, as appropriate. Changes in the proportions over time were examined using the Bhapkar test, followed by the McNemar test for aggregated categories. All *p*-values ≤0.05 were considered statistically significant. All data were analyzed using SAS software (version 9.4; SAS Institute Inc.).

RESULTS

Study population

A total of 190 infants were enrolled in the study; 183 infants were included in the safety population and 157 infants were included in the digestive tolerance population (**Fig. 1**). The

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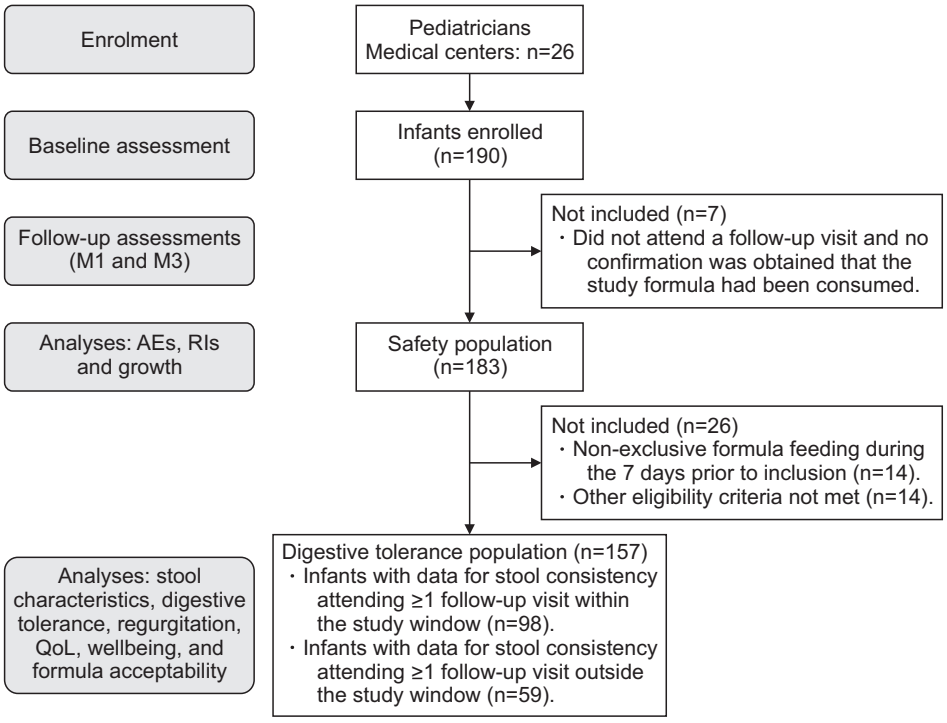

Fig. 1. Participant flow through the study.
AE: adverse event, RI: respiratory infection, QoL: quality of life.

dropout rate was 9.5% (18/190), with the most common reasons being loss to follow-up (n=6, 33.3%), parental decisions, poor acceptability of the formula, and ineffectiveness of the formula for regurgitation (n=2 for each reason, 11.1%) (**Supplementary Table 2**).

Demographic and clinical characteristics of the study populations at baseline

The baseline demographic characteristics of the two study populations are presented in **Supplementary Table 3.** At inclusion, approximately 98% of the infants in both populations were below 4 months of age, and the vast majority (87.5%) were fed standard infant formula.

The clinical and anthropometric characteristics of the study population at baseline are shown in **Table 1** and **Supplementary Table 4**. The mean stool frequency at baseline was 2.6 (SD:1.3) stools per day, with consistency reported as loose in approximately half of all cases (49.7%) and formed in 20.4% of cases. At baseline, nearly all infants (96.8%) regurgitated at least three times per day, and 72.0% had more than five regurgitation episodes per day or regurgitated small amounts after every meal. Colic was the most frequently reported associated digestive symptom, present in approximately half of the infants (53.2%), followed by constipation (10.3%) and diarrhea (8.3%). Crying, assessed as an indicator of infant QoL, was reported to have lasted for more than 1 hour in 70.7% of the cases at baseline.

Evolution of stool frequency and consistency, and digestive symptoms

Overall, the mean stool frequency per day decreased between baseline and M1: Δ=−0.3 (95% confidence interval [CI], −0.5; −0.1, p=0.016) and between baseline and M3: Δ=−0.7 (95% CI, −1.0; −0.5, p<0.0001). The proportion of infants who passed one or two stools per day increased during the study period from 44.3% at baseline to 82.7% at M3. By M1 and M3, none

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Table 1. Stool frequency and consistency, digestive symptoms, regurgitation severity, and crying over the study period

Characteristics	Baseline	Month 1	Month 3	*p*-values	
		N=157		ΔM1–baseline	ΔM3–baseline
Stool frequency (d)	n=140	n=134	n=110	n=122	n=100
<1	3 (2.1)	0 (0.0)	0 (0.0)	0.016‡	<0.0001‡
1–2	62 (44.3)	83 (61.9)	91 (82.7)		
3–4	65 (46.4)	44 (32.8)	19 (17.3)		
5–6	9 (6.4)	7 (5.2)	0 (0.0)		
>7	1 (0.7)	0 (0.0)	0 (0.0)		
Stool consistency*	n=157	n=157	n=135	n=157	n=135
Hard	25 (15.9)	3 (1.9)	5 (3.7)	0.079§	0.748§
Formed	32 (20.4)	48 (30.6)	63 (46.7)		
Loose	78 (49.7)	89 (56.7)	59 (43.7)		
Watery	22 (14.0)	17 (10.8)	8 (5.9)		
Diarrhea	n=156	n=155	n=135	n=154	n=134
Yes	13 (8.3)	16 (10.3)	4 (3.0)	0.559§	0.180§
Constipation	n=156	n=153	n=135	n=152	n=134
Yes	16 (10.3)	3 (2.0)	7 (5.2)	0.001§	0.302§
Colic	n=156	n=152	n=134	n=152	n=133
Yes	83 (53.2)	44 (28.9)	11 (8.2)	<0.0001§	<0.0001§
Regurgitation severity†	n=157	n=157	n=135	n=157	n=135
0: 0 to 2 episodes a day	5 (3.2)	59 (37.6)	89 (65.9)	<0.0001‖	<0.0001‖
1: 3 to 5 episodes per day with small amounts	28 (17.8)	67 (42.7)	39 (28.9)		
2: More than 5 episodes per day with amounts equivalent to more than one teaspoon	43 (27.4)	21 (13.4)	5 (3.7)		
3: More than 5 episodes per day with amounts equivalent to about half of the meal for less than half of the meals	32 (20.4)	8 (5.1)	1 (0.7)		
4: Continuous regurgitation of small amounts more than 30 minutes after each meal	38 (24.2)	1 (0.6)	1 (0.7)		
5: Regurgitation of half to the total amount of a meal for at least half of the meals	8 (5.1)	1 (0.6)	0 (0.0)		
6: Regurgitation of the "whole meal" after each meal	3 (1.9)	0 (0.0)	0 (0.0)		
Crying during the past 24 h	n=157	n=155	n=135	n=155	n=135
No crying	7 (4.5)	30 (19.4)	58 (43.0)	<0.0001§	<0.0001§
<1 h	39 (24.8)	86 (55.5)	62 (45.9)		
1–2 h	56 (35.7)	31 (20.0)	14 (10.4)		
2–3 h	39 (24.8)	6 (3.9)	1 (0.7)		
>3 h	16 (10.2)	2 (1.3)	0 (0.0)		

Values are presented as number (%).
M1: month 1, M3: month 3, d: days, N: number of infants in the entire study population, n: number of infants for which data were collected.
*Stool consistency was assessed using the Brussels Infant and Toddler Stool Scale [24,25].
†Regurgitation severity was assessed using the Adapted Vandenplas scale [14,26].
p-values for the changes from baseline at months 1 and 3 were calculated using either the ‡Paired *t*-test, §Wilcoxon signed-rank test or ‖Bhapkar test.

of the infants passed fewer than one stool or more than three or four stools per day (**Fig. 2A** and **Table 1**).

At all three study visits, most infants were reported to have passed loose or formed stool (**Fig. 2B**), without statistically significant differences between visits (M1 vs. baseline, p=0.079; M3 vs. baseline, p=0.748; **Table 1**). The use of the study formula did not increase the number of infants passing watery stools (14.0% at baseline, 10.8% at M1, and 5.9% at M3) or hard stools (15.9% at baseline, 1.9% at M1, and 3.7% at M3). Analysis of the normalization of stool consistency during the study period (i.e., the number of infants passing loose or formed stools according to the Brussels Infant and Toddler Stool Scale [25]) revealed that among infants with watery or hard stools at baseline (n=47), an improvement in the stool consistency towards loose or formed stools was observed in 87.2% of cases (n=41) at M1 and in 80.9% of cases (n=38) at M3. Among the 110 infants who had loose or formed stools at baseline, this consistency was maintained in 87.3% (n=96) at M1 and 76.4% (n=84) at M3.

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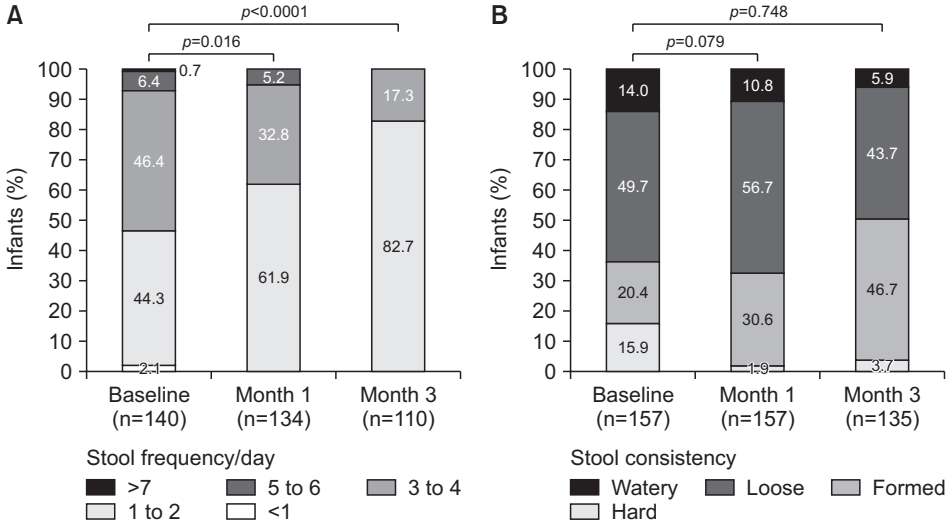

Fig. 2. Stool frequency and composition at the baseline and follow-up visits. The data represent the percentage of infants in each of the stool frequency (A) and stool consistency (B) categories at each study visit based on parental recall over the past 24 hours. *p*-values were calculated for changes from baseline at 1 and 3 months. n: number of infants for whom data were available.

The incidence of diarrhea was low, reported in 8.3% of the infants at baseline and 10.3% and 3.0% at M1 and M3, respectively, and no statistically significant changes from baseline were observed at any of the follow-up time points (M1 vs. baseline, p=0.559; M3 vs. baseline, p=0.180; **Table 1**). The number of infants with constipation decreased significantly from 10.3% at baseline to 2.0% at M1 (p=0.001). There was no significant difference in the occurrence of constipation at M3 (5.2%) compared with that at baseline (p=0.302; **Table 1**). Finally, the number of infants with colic significantly decreased from 53.2% at baseline to 28.9% at M1 and 8.2% at M3 (p<0.001 for both time points; **Table 1**).

Impact of the study formula on regurgitation

Use of the study formula was associated with a significant decrease in the severity of regurgitation in 83.4% of infants at M1 and 92.6% of infants at M3 (**Fig. 3**). The proportion of infants with regurgitation severity scores ≤1 (regurgitating only small amounts of formula, <5 times a day) increased from 21.0% at baseline to 80.3% at M1 and 94.8% at M3 (M1 vs. baseline, p<0.001; M3

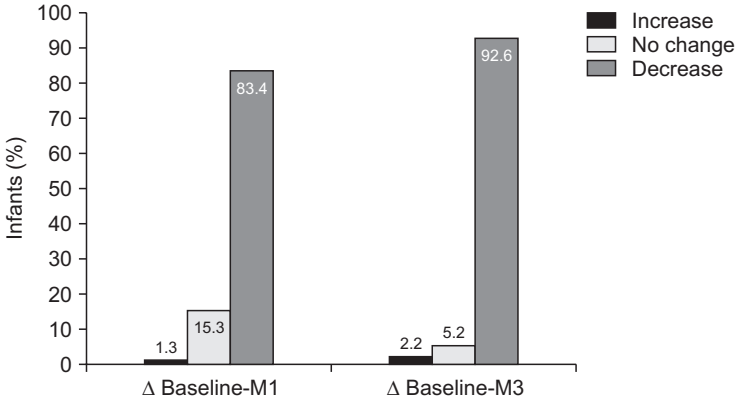

Fig. 3. Change in the number of regurgitation episodes over the study period. The data represent the percentage of infants with a reported increase, no change, or decrease in the number of regurgitation episodes per day between baseline and M1 (n=157) and between baseline and M3 (n=135).
M1: month 1, M3: month 3.

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vs. baseline, $p<0.001$), whereas the number of infants with more severe regurgitation (scores of 2 to 4 with >5 regurgitation episodes per day or regurgitating small amounts after every meal) decreased from 72.0% at baseline to 19.1% at M1 and 5.1% at M3 (**Table 1**).

Acceptability of the study formula and its impact on infant QoL and wellbeing

Most parents indicated that the study formula was well-or very well-accepted by their infants at M1 (91.7%, 143/156) and M3 (97.8%, 132/135). Moreover, 80.2% of parents (125/156) at M1 and 92.6% (125/135) at M3 indicated that the study formula was easily digested by their infants. In addition, 74.0% of the parents (111/150) at M1 and 87.7% (107/122) at M3 indicated that they were satisfied or very satisfied with the consistency of their infants' stools.

Crying decreased over the course of the study ($p<0.001$), and the number of infants crying for less than 1-hour during the previous 24-hour period increased from 29.3% at baseline to 74.9% at M1 and 88.9% at M3 (**Table 1**). The majority of parents also reported that their infants slept well after being fed with the study product (79.5% [124/156] at M1 and 93.3% [126/135] at M3). Most parents (94.0%; 142/151) felt that the well-being of their infants had improved between baseline and M1, and 86.6% (116/134) felt that infant well-being had improved between M1 and M3.

Safety of the study formula

A total of 22 AEs were reported in 16 of 183 infants in the safety population. GI disorders were the most common AEs (n=17), the most frequent being soft stools (n=4), constipation (n=4), infantile colic (n=3), and flatulence (n=2). Upper or lower respiratory infections (n=46) occurred in 20.2% of the infants in the safety population (37/183), with the most common infections being bronchiolitis (n=18) and nasopharyngitis (n=17).

The weight, length, and head circumference of infants in the safety population (N=183) increased over the study period, with median z scores in the interval [−1,+1] for most infants by M3 (**Supplementary Table 4**).

DISCUSSION

This multicenter, observational, prospective study involving infants with regurgitation, but who were otherwise healthy, demonstrated that a thickened AR infant formula containing LBG, prebiotics, and postbiotics was well tolerated and raised no safety concerns when used over a 3-month period in a real-world setting. Stool frequency and consistency remained within the normal physiological range, whereas regurgitation, colic, infant crying, and parental perceptions of infant well-being improved after 1 month of using the study formula. The levels of parental satisfaction and infant acceptance of the formula were high, and the participating infants showed adequate growth. The incidence of AEs, including GI symptoms and respiratory infections, was low, and the types of AEs reported were consistent with that expected in the study population.

The results of this observational study support those of a previous RCT [17], which demonstrated that the AR formula containing LBG, prebiotics, and postbiotics was safe, well tolerated, and reduced regurgitation and the overall GI burden. The current study showed that the AR formula led to a reduction in the severity of regurgitation in 83.4% of infants after only one month of use, thus confirming the high level of effectiveness of LBG-thickened

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AR formulas for managing regurgitation observed in numerous previous studies [10,13,15]. In addition, this study demonstrated that the benefits of the formula for improving GI symptoms beyond FGID were maintained in a real-world setting throughout the study.

As in the RCT [17] and other previous studies [2,3,27], several infants with regurgitation included in the current study (>50%) also had other digestive symptoms, most commonly colic. Management of multiple symptoms is essential because the presence of more than one FGID is associated with poorer QoL and sleep quality, and increased levels of parental anxiety [28]. Immaturity of the GI system and dysbiosis of the gut microbiota are believed to contribute to the onset of FGIDs during early infancy [29,30]. The effect of the study formula on the alleviation of GI symptoms beyond regurgitation may be associated with the effect of the combination of prebiotics, scGOS/lcFOS, and postbiotics on the gut microbiota. Indeed, previous studies have indicated that infant formulas containing a combination of scGOS/lcFOS and postbiotics have a beneficial effect on the gut microbiota, leading to microbiome composition and metabolic activity in healthy formula-fed infants that more closely resemble those found in breastfed infants [19,22].

This study also indicated that the use of the study formula was associated with normal stool outcomes in infants with regurgitation. Stool frequency and consistency are highly variable in young infants and are influenced by the type of feeding, with exclusively breastfed infants tending to pass softer stools more frequently than exclusively formula-fed infants [31]. The addition of prebiotics to non-thickened formula softens stools in healthy formula-fed infants [32,33]. Similarly, the thickening agent LBG, contains indigestible glycosidic polymers that may act as a source of vegetable fibers and have a prebiotic effect [13]. Use of the formula containing both prebiotics and LBG in the current study was associated with all infants passing between 1 and 4 stools per day at the 3-month visit, which was within the range reported for healthy term-born infants fed a non-thickened formula with prebiotics and postbiotics (approximately 2 stools per day [20,21]), but was lower than that reported for exclusively breastfed infants (3 to 5 stools per day [31]). The participating infants also had mostly loose or formed stool types, both of which were considered normal according to the Brussels Infant and Toddler Stool Scale [25]. Stool consistency was also in the range of that previously described in healthy term-born infants who received a non-thickened formula containing prebiotics and postbiotics [20]. In a previous study, the stool consistency of infants who received pre- and postbiotic-containing formulas was reported to be closer to that observed in breastfed infants [20]. This study showed that formula use was not associated with an increase in the number of infants passing watery or hard stools. Additionally, the incidence of diarrhea and constipation was low.

The current recommendations for managing FGIDs are to provide parental reassurance and education, with nutritional advice being preferred over pharmacological treatments to limit the risk of AEs [4]. This strategy aims to break the cycle of infant distress, parental concern, anxiety, repeated medical consultations, inappropriate pharmacological interventions, and escalating healthcare and personal costs associated with FGIDs and GI discomfort [8,9,34]. The findings of the current study showed that the formula addressed the most frequent concerns raised by the parents of infants with FGIDs and GI symptoms. In addition to relieving infant regurgitation and colic, most parents reported being satisfied or very satisfied with their infant's acceptance and ease of digestion of the formula and with the consistency of their infant's stools. After only one month of formula use, most parents reported improvements in infant well-being and sleep quality.

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In the assessment of family centered outcomes, crying was also found to decrease during the first month of formula use. A systematic review of studies assessing the impact of infant crying on new mothers concluded that mothers of infants who cried frequently were more likely to experience tiredness and fatigue, triggering depressive symptoms, concentration problems, frustration, and hampering parent-child interactions [34]. Excessive crying in infancy may also lead to long-term parental perceptions of child vulnerability, which may be associated with a more frequent need for healthcare interventions [35], an increased likelihood of behavioral and sleeping problems in toddlers [36], and poorer mental health in school-age children [35]. Early management, which may help manage infant crying associated with FGIDs and GI symptoms, is, therefore, essential for promoting the short-term and long-term health and well-being of children and their families.

Finally, before consuming the study formula, anthropometric data indicated that the average weight and length of our cohort of infants with regurgitation were somewhat below the age- and sex-adjusted WHO standards. This finding is in line with that of a previous study in a population of healthy French infants without regurgitation [37]. However, all growth parameters were within the expected range after 3 months of using the study formula.

This study provides the first evaluation of the use of a new AR formula with prebiotics and postbiotics in a real-world setting, with assessments of family centered outcomes, broader parameters, such as infant well-being and growth, and the safety and digestive tolerance of the formula over a longer 3-month period compared with the shorter study durations generally used in previous studies with AR formulas. The main limitation of this real-world design was the lack of a control group, which would have allowed the assessment of how digestive symptoms and FGIDs evolved naturally over the course of the study. Indeed, colic, crying, and sleep quality have been found to improve naturally from approximately three months of age [4,38,39], whereas the prevalence of regurgitation has been reported to peak at approximately three to four months of age [40]. Importantly, no increase in the severity of any of these symptoms was observed after the administration of this formula. All these symptoms improved. As the mean age of the infants included in this study was approximately 2 months and the beneficial effects of the formula on GI symptoms were observed after only 1 month of use, the findings indicate that the formula contributed to the improvement in GI symptoms at a stage when they would not have been expected to begin to resolve naturally. Generally, it should also be noted that the 3-month follow-up used in our study provides valuable and much-needed real-world data on the long-term evolution of gastrointestinal symptoms in infants with uncomplicated infantile regurgitation managed according to the current practice guidelines, as well as on the impact of current management practices on family centered outcomes. In addition, although stool consistency and regurgitation severity were assessed using validated assessment tools, the data were based on parental recall over the past 24 hours and therefore, may be subject to recall bias. Nonetheless, our findings are consistent with the effects on regurgitation and improvement of wider GI symptoms seen in previous studies with AR formulas with LBG and prebiotics and/or postbiotics in infants with regurgitation [15,17].

In conclusion, this study demonstrated that a new thickened AR formula containing LBG, prebiotics, and postbiotics showed good digestive tolerance, supported adequate growth, and had a good safety profile in infants with regurgitation in a real-world setting over a 3-month period. Stool frequency and consistency were within the ranges previously observed in healthy formula-fed infants, and improvements in regurgitation severity and in GI symptoms beyond regurgitation were observed. Moreover, parental satisfaction and infant

acceptability of the formula were high, and assessments of crying and infant well-being suggested that the formula helped address broader family centered issues associated with FGIDs and GI discomfort. AR formulas with LBG, prebiotics, and postbiotics could therefore potentially provide an effective strategy for the management of infant regurgitation and the associated GI discomfort.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1
Study inclusion and exclusion criteria

Click here to view

Supplementary Table 2
Study terminations

Click here to view

Supplementary Table 3
Demographic characteristics of the study populations at baseline

Click here to view

Supplementary Table 4
Anthropometric parameters at baseline and at the follow-up visits

Click here to view

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Subject No. :

Inclusion questionnaire: Pediatrician (Visit 1: baseline)

☐ After being informed of the follow-up procedures, data processing methods, and aims of the study, the parent(s) or guardian(s) have given their informed consent for the infant to be included in the study.

Consultation date: |__|__| / |__|__| / |__|__|__|__| Surname: |__|__| (First two letters) First name: |__|__| (First two letters)

Did the subject meet all of the inclusion criteria and none of the exclusion criteria? ☐ No ☐ Yes

Demographic characteristics:

Sex: ☐ Male ☐ Female Age: |__|__| Weeks Height: |__|__|__| cm Weight: |__|__|__|__| g

Birth Weight: |__|__|__|__| g Head circumference: |__|__| cm

Feeding characteristics at inclusion:

Duration of exclusive breastfeeding/mixed feeding : ☐ Less than 1 month ☐ 1 month + ☐ 2 months + ☐ 3 months +

Formula feeding history ☐ Standard stage 1 formula ☐ Anti-regurgitation formula

Number of bottles of formula consumed by the infant in 24 hrs: |__|__|

☐ ¼ of the bottle or less ☐ ½ of the bottle ☐ ¾ of the bottle ☐ all of the bottle

Digestive symptom characteristics:

How severe was the infant's regurgitation over the past 24 hrs? **Please provide a score (from 0 to 6) based on the definitions provided below.**

Tick one box	Score	Regurgitation
☐	0	0 to 2 episodes per day.
☐	1	3 to 5 times per day with small amounts.
☐	2	More than 5 episodes per day with amounts equivalent to more than one teaspoon.
☐	3	More than 5 episodes per day with amounts equivalent to about half of the meal for less than half of the meals.
☐	4	Continuous regurgitation of small amounts more than 30 minutes after each meal.
☐	5	Regurgitation of half to the total amount of a meal for at least half of the meals.
☐	6	Regurgitation of the "whole meal" after each meal.

Number of stools during the last 24 hrs: |__|__|

Average consistency of the stools during the past 24 hrs (please show the photos below to the parent(s) or guardian(s)):

☐ Hard stools

☐ Formed stools

☐ Loose stools

☐ Watery stools

Diarrhea during the last 24 hrs: ☐ No ☐ Yes

Constipation during the last 24 hrs: ☐ No ☐ Yes

Colic during the last 24 hrs: ☐ No ☐ Yes

Infant quality of life

Crying during the last 24 hrs: ☐ No crying ☐ Less than 1 hr ☐ 1 to 2 hrs ☐ 2 to 3 hrs ☐ More than 3 hrs

You have now completed the pediatrician inclusion questionnaire (Visit 1 - baseline).
Please ensure that you:

1. **return the completed questionnaire, in the envelope provided, as soon as possible**
2. **make an appointment with the parent(s) or guardian(s) for the follow-up visit in 1 month (M1)**

This document should only be filled in by a healthcare professional.

This document should only be filled in by a healthcare professional

Follow-up questionnaire: Pediatrician (Visit 2: M1)

Subject No. :

Consultation date: |__|__| / |__|__| / |__|__|__|__| Surname: |__|__| (First two letters) First name: |__|__| (First two letters)

Infant growth:

Weight: |__|__|__|__| g Height: |__|__|__| cm Head circumference: |__|__| cm

Digestive symptom characteristics:

How severe was the infant's regurgitation over the past 24 hrs? **Please provide a score (from 0 to 6) based on the definitions provided below.**

Tick one box	Score	Regurgitation
☐	0	0 to 2 episodes per day.
☐	1	3 to 5 times per day with small amounts.
☐	2	More than 5 episodes per day with amounts equivalent to more than one teaspoon.
☐	3	More than 5 episodes per day with amounts equivalent to about half of the meal for less than half of the meals.
	4	Continuous regurgitation of small amounts more than 30 minutes after each meal.
☐	5	Regurgitation of half to the total amount of a meal for at least half of the meals.
☐	6	Regurgitation of the "whole meal" after each meal.

Number of stools during the last 24 hrs: |__|__|

Average consistency of the stools during the past 24 hrs (please show the photos below to the parent(s) or guardian(s)):

☐ Hard stools

☐ Formed stools

☐ Loose stools

☐ Watery stools

Appendix 1. Study questionnaires.

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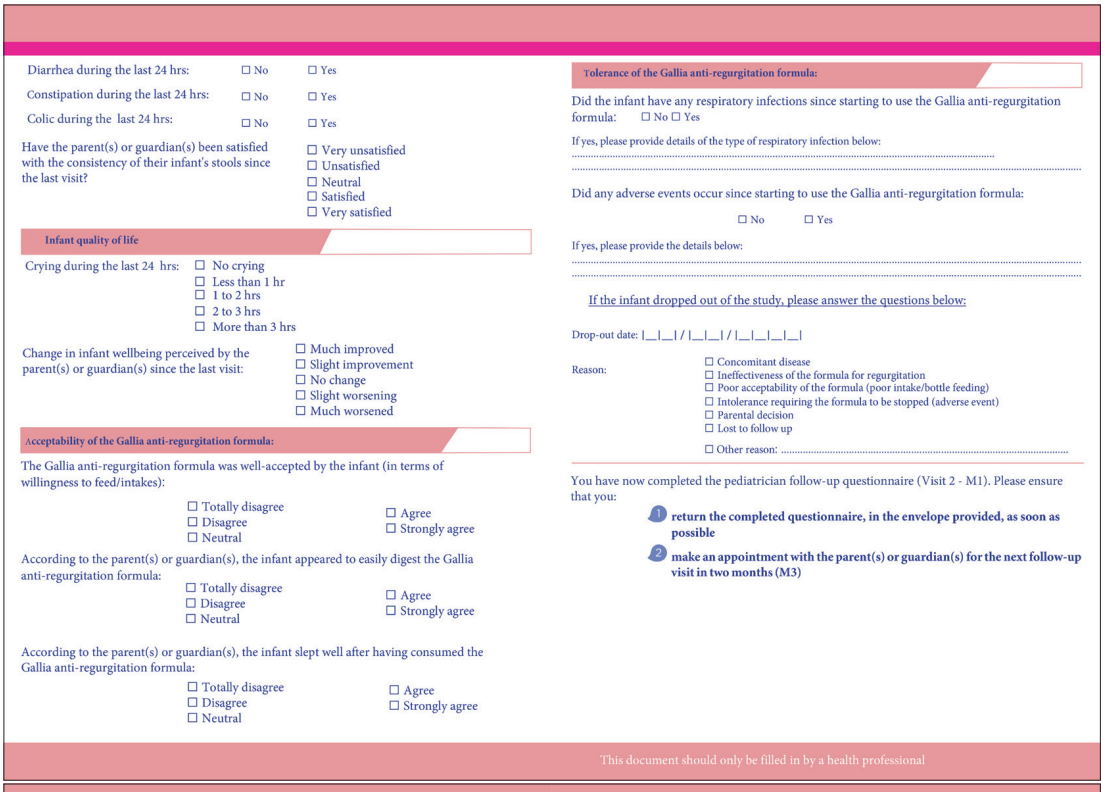

Diarrhea during the last 24 hrs: ☐ No ☐ Yes

Constipation during the last 24 hrs: ☐ No ☐ Yes

Colic during the last 24 hrs: ☐ No ☐ Yes

Have the parent(s) or guardian(s) been satisfied with the consistency of their infant's stools since the last visit?
☐ Very unsatisfied
☐ Unsatisfied
☐ Neutral
☐ Satisfied
☐ Very satisfied

Infant quality of life

Crying during the last 24 hrs:
☐ No crying
☐ Less than 1 hr
☐ 1 to 2 hrs
☐ 2 to 3 hrs
☐ More than 3 hrs

Change in infant wellbeing perceived by the parent(s) or guardian(s) since the last visit:
☐ Much improved
☐ Slight improvement
☐ No change
☐ Slight worsening
☐ Much worsened

Acceptability of the Gallia anti-regurgitation formula:

The Gallia anti-regurgitation formula was well-accepted by the infant (in terms of willingness to feed/intakes):
☐ Totally disagree ☐ Disagree ☐ Neutral ☐ Agree ☐ Strongly agree

According to the parent(s) or guardian(s), the infant appeared to easily digest the Gallia anti-regurgitation formula:
☐ Totally disagree ☐ Disagree ☐ Neutral ☐ Agree ☐ Strongly agree

According to the parent(s) or guardian(s), the infant slept well after having consumed the Gallia anti-regurgitation formula:
☐ Totally disagree ☐ Disagree ☐ Neutral ☐ Agree ☐ Strongly agree

Tolerance of the Gallia anti-regurgitation formula:

Did the infant have any respiratory infections since starting to use the Gallia anti-regurgitation formula: ☐ No ☐ Yes

If yes, please provide details of the type of respiratory infection below:
.....
.....

Did any adverse events occur since starting to use the Gallia anti-regurgitation formula:
☐ No ☐ Yes

If yes, please provide the details below:
.....
.....

If the infant dropped out of the study, please answer the questions below:

Drop-out date: |__|__| / |__|__| / |__|__|__|__|

Reason:
☐ Concomitant disease
☐ Ineffectiveness of the formula for regurgitation
☐ Poor acceptability of the formula (poor intake/bottle feeding)
☐ Intolerance requiring the formula to be stopped (adverse event)
☐ Parental decision
☐ Lost to follow up
☐ Other reason: .....

You have now completed the pediatrician follow-up questionnaire (Visit 2 - M1). Please ensure that you:

1. **return the completed questionnaire, in the envelope provided, as soon as possible**
2. **make an appointment with the parent(s) or guardian(s) for the next follow-up visit in two months (M3)**

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This document should only be filled in by a healthcare professional

Follow-up questionnaire: Pediatrician (Visit 3: M3)

Subject No. :

Consultation date: |__|__| / |__|__| / |__|__|__|__| Surname: (First two letters) |__|__| First name: (First two letters) |__|__|

Infant growth:

Weight: |__|__|__|__| g Height: |__|__|__| cm Head circumference: __|__| cm

Digestive symptom characteristics:

How severe was the infant's regurgitation over the past 24 hrs? **Please provide a score (from 0 to 6) based on the definitions provided below.**

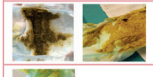
Tick a box	Score	Regurgitation
☐	0	0 to 2 episodes per day.
☐	1	3 to 5 times per day with small amounts.
☐	2	More than 5 episodes per day with amounts equivalent to more than one teaspoon
☐	3	More than 5 episodes per day with amounts equivalent to about half of the meal for less than half of the meals.
☐	4	Continuous regurgitation of small amounts more than 30 minutes after each meal.
☐	5	Regurgitation of half to the total amount of a meal for at least half of the meals.
☐	6	Regurgitation of the "whole meal" after each meal.

Number of stools during the last 24 hrs:|__|__|

Average consistency of the stools during the past 24 hrs (please show the photos below to the parent(s) or guardian(s)):

☐ Hard stools

☐ Formed stools



☐ Loose stools

☐ Watery stools

Appendix 1. (Continued) Study questionnaires.

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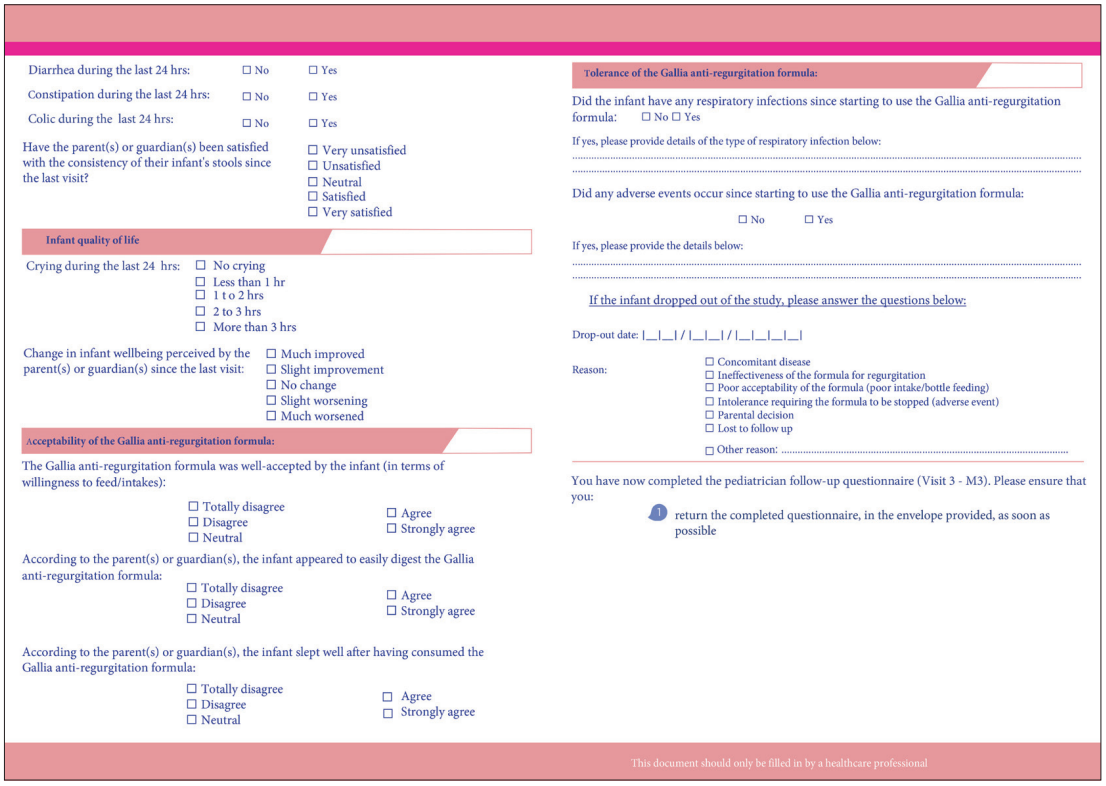

Diarrhea during the last 24 hrs: ☐ No ☐ Yes

Constipation during the last 24 hrs: ☐ No ☐ Yes

Colic during the last 24 hrs: ☐ No ☐ Yes

Have the parent(s) or guardian(s) been satisfied with the consistency of their infant's stools since the last visit?
☐ Very unsatisfied
☐ Unsatisfied
☐ Neutral
☐ Satisfied
☐ Very satisfied

Infant quality of life

Crying during the last 24 hrs:
☐ No crying
☐ Less than 1 hr
☐ 1 to 2 hrs
☐ 2 to 3 hrs
☐ More than 3 hrs

Change in infant wellbeing perceived by the parent(s) or guardian(s) since the last visit:
☐ Much improved
☐ Slight improvement
☐ No change
☐ Slight worsening
☐ Much worsened

Acceptability of the Gallia anti-regurgitation formula:

The Gallia anti-regurgitation formula was well-accepted by the infant (in terms of willingness to feed/intakes):
☐ Totally disagree
☐ Disagree
☐ Neutral
☐ Agree
☐ Strongly agree

According to the parent(s) or guardian(s), the infant appeared to easily digest the Gallia anti-regurgitation formula:
☐ Totally disagree
☐ Disagree
☐ Neutral
☐ Agree
☐ Strongly agree

According to the parent(s) or guardian(s), the infant slept well after having consumed the Gallia anti-regurgitation formula:
☐ Totally disagree
☐ Disagree
☐ Neutral
☐ Agree
☐ Strongly agree

Tolerance of the Gallia anti-regurgitation formula:

Did the infant have any respiratory infections since starting to use the Gallia anti-regurgitation formula: ☐ No ☐ Yes

If yes, please provide details of the type of respiratory infection below:
.....
.....

Did any adverse events occur since starting to use the Gallia anti-regurgitation formula:
☐ No ☐ Yes

If yes, please provide the details below:
.....
.....

If the infant dropped out of the study, please answer the questions below:

Drop-out date: |__|__| / |__|__| / |__|__|__|__|

Reason:
☐ Concomitant disease
☐ Ineffectiveness of the formula for regurgitation
☐ Poor acceptability of the formula (poor intake/bottle feeding)
☐ Intolerance requiring the formula to be stopped (adverse event)
☐ Parental decision
☐ Lost to follow up
☐ Other reason: .....

You have now completed the pediatrician follow-up questionnaire (Visit 3 - M3). Please ensure that you:
1 return the completed questionnaire, in the envelope provided, as soon as possible

This document should only be filled in by a healthcare professional

Appendix 1. (Continued) Study questionnaires.

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