BACKGROUND: Constipation is a frustrating symptom affecting 3% of children worldwide. A fermented dairy product containing *Bifidobacterium lactis* strain DN-173 010 was effective in increasing stool frequency in constipated women. Our aim was to assess the effects of this product in constipated children. There is currently insufficient evidence to recommend fermented dairy products containing *B. lactis* strain DN-173 010 for these patients.

WHAT THIS STUDY ADDS: In constipated children, the fermented dairy product that contained *B lactis* strain DN-173 010 increased stool frequency, but this increase was comparable to that of the control group. There is currently insufficient evidence to recommend fermented dairy products that contain *B lactis* strain DN-173 010 for these patients.

RESULTS: Eleven children did not return to any follow-up visit (5 in the probiotic group, 6 in the control group) and were therefore excluded from the final analysis. Thus, 74 children in each group were analyzed. The change in stool frequency from baseline to after 3 weeks of product consumption increased in both groups, but the difference was not statistically significant (2.9 ± 3.2 in probiotic group versus 2.6 ± 2.6 in control group, *P* = .35). There were no serious adverse events.

CONCLUSIONS: In constipated children, the fermented dairy product containing *B lactis* strain DN-173 010 did increase stool frequency, but this increase was comparable in the control group. There is currently not sufficient evidence to recommend fermented dairy products containing *B lactis* strain DN-173 010 in this category of patients. Future studies should focus on whether a longer period of probiotic products is more effective in children who have a short history of constipation.

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**ABBREVIATIONS**

IBS—irritable bowel syndrome

CFU—colony-forming U

CI—confidence interval

LGG—*Lactobacillus rhamnosus* GG

This trial has been registered at www.clinicaltrials.gov (identifier NTRTC1571).

Prof Szajewska and Dr Benninga contributed equally to this work.

All authors participated in the design of the study, and read and approved the final manuscript; Drs Chmielewska and Tabbers and Miss Roseboom collected the data; Drs Reitsma and Tabbers did the statistical analysis; Dr Tabbers drafted the first manuscript; and Prof Szajewska and Dr Benninga supervised the current study.

Dr Tabbers had full access to all of the data and takes full responsibility for the veracity of the data and analysis.

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Chronic constipation is a common problem in childhood, with an estimated prevalence of 3% in the Western world.\(^1\) Constipation is a debilitating condition characterized by infrequent painful defecation, faecal incontinence, and abdominal pain.\(^2\) The pathophysiology underlying functional constipation is undoubtedly multi-factorial, and not well understood. Withholding behavior is probably the major cause for the development of constipation.\(^2\) A study in a tertiary hospital showed that despite intensive medical and behavioral therapy, 30% of patients who developed constipation before the age of 5 years continued to have severe complaints of constipation beyond puberty.\(^3\)

In a recent systematic review in which the effects of using laxative treatment and dietary measures were evaluated for the treatment of childhood constipation, it was shown that there is insufficient evidence to suggest that laxative treatment is better than placebo in children with constipation because of a lack of placebo-controlled trials.\(^4\)

Probiotics are defined as live microorganisms which when administered in adequate amounts might improve the health of the host.\(^5\) A dysbiosis in the gut microbiota has been suggested as a mechanism behind constipation that might improve after the ingestion of probiotics. Furthermore, probiotics can lower the pH of the colon by producing lactic acid, acetic acid, and other acids. A lower pH enhances colonic peristalsis and, subsequently, decreases the colonic transit time.\(^6,7\) Two randomized, placebo-controlled trials with the fermented dairy product containing *Bifidobacterium lactis* DN-173 010 have been performed: 1 in adult patients with irritable bowel syndrome (IBS) and constipation, and 1 in constipated women with a defecation frequency <3 times per week. Both trials showed a significant increase in stool frequency in the probiotic group compared with the control group in subjects presenting <3 stools per week.\(^8,9\) No adverse events were reported. Therefore, we conducted a multicenter, randomized, double-blind, controlled trial to assess the effects of this specific probiotic product in children with constipation.

**METHODS**

**Patients**

This was a prospective double-blind, placebo-controlled randomized multicenter, 2-nation (Netherlands and Poland) trial. The design and rationale of the study have been described in detail elsewhere.\(^10\) Consecutive children, aged 3 to 16, were enrolled in 3 academic hospitals (Netherlands and Poland) and 12 Dutch nonacademic hospitals. Patients were eligible to be randomly assigned if they had been suffering from functional constipation according to Rome III criteria for the last 2 months.\(^11,12\) They had a defecation frequency of <3 times per week and 1 or more of the following criteria: faecal incontinence >1 episode per week, a large amount of stools that clog the toilet, painful defecation, withholding behavior, or abdominal or rectal faecal impaction on physical examination. Children had to be familiar with consumption of dairy products. Exclusion criteria were treatment for constipation <2 weeks before the start of the study, a diagnosis of either IBS or functional nonretentive faecal incontinence according to Rome III criteria, a diagnosis of mental retardation or metabolic disease (hypothyroidism), Hirschsprung disease, spinal anomalies, anorectal pathology, previous gastrointestinal surgery, lactose intolerance or known allergy to a product component, treatment with antibiotics in the previous month, or treatment with medication that influences gastrointestinal motility (e.g., cisapride). Eligible patients were randomly assigned. Random numbers were generated by a computer program with an allocation ratio of 1:1 and with well-balanced blocks. Separate lists were generated for each study site. All investigators were unaware of product allocation. The randomization lists were kept confidential by the person responsible for the preparation of the study products and their labeling. All children and/or their legal guardians gave written informed consent to participate in the study. This study was investigator-initiated and investigator-driven and performed in accordance with the principles of the Declaration of Helsinki and good clinical practice guidelines. The independent ethics committees of all participating hospitals approved the protocol.

**Study Products**

The 2 study products were identical in weight, color, smell, taste, and packaging. All doctors, research staff, and patients with their caregivers involved remained unaware of the product administered to the patient. The probiotic product consisted of the fermented milk Activia (125-g pot containing <5 g of lactose) manufactured with lactic cultures including *B. lactis* DN-173 010 (strain number I-2494 in French National Collection of Cultures of Microorganisms [CNCM, Paris, France]) at least 4,25 × 10^9 colony-forming U [CFU] per pot), yogurt starter cultures (*Lactobacillus delbrueckii* spp. *Bulgarius* CNCM strain numbers I-1632 and I-1519, and *Streptococcus thermophilus* CNCM strain number I-1630, at least 1.2 × 10^9 CFU per pot) and *Lactococcus cremoris* (CNCM strain number I-1631). The control product consisted of a milk-based, nonfermented dairy product (125-g pot) without probiotics and with a low content of lactose (<2.5 g per pot). Both the probiotic and control preparations were checked according to national regulations for any...
contamination with known pathogens and macronutrient composition including lactose. Before the start and at the end of the study, the test product was analyzed by counting *B. lactis* DN-173 010 (at least 4.25 × 10⁹ CFU per pot) and *Streptococcus thermophilus* and *Lactobacillus bulgaricus* (at least 1.2 × 10⁹ CFU per pot).

Every patient had to take 2 pots per day: 1 at breakfast and 1 at the evening meal for 3 consecutive weeks. Products were kept in the refrigerator.

The study period was 5 weeks with 3 clinic appointments: inclusion visit (V1), randomization visit (V2), and clinical evaluation visit (V3) (Fig 1). The first week was used to obtain baseline values, followed by a period of 3 days where enemas were given. Patients were then treated for 3 weeks with the study products. Products were delivered to homes by study nurses using cool packages. The last visit was after 3 weeks of product consumption (Fig 1).

During the study, all children were instructed to try to defeate on the toilet for 5 to 10 minutes after each meal and to complete daily a standardized bowel diary. Intake of any other fermented dairy product or yoghurt was not allowed. Names of these products were pointed out in the diary. During the product consumption period, patients were instructed to take 5 mg bisacodyl if they did not defeate for 3 consecutive days.

Investigators checked all diaries of the participants for compliance. Subjects had to complete the number of study products consumed for each day. Furthermore, all patients were asked to return the remaining unused pots.

**Outcomes**

Frequency of defecation, frequency of faecal incontinence episodes, self-evaluation of digestive symptoms (abdominal pain and flatulence on a 2-point scale with 1, yes; 2, no), and self-evaluation of adverse effects (nausea, diarrhea and bad taste on a 2-point scale with 1, yes; 2, no) were assessed daily using a subject diary. Stool consistency and pain during defecation (2-point scale, with 1, yes; 2, no) were assessed for each passed stool using the same diary. Stool consistency was scored using the 7-point Bristol stool scale in which a score of 1 describes stools that are hard lumps, a score of 4 describes stools that are normal (smooth and soft), and a score of 7 describes stools that are watery stools (diarrhea). The diary was also used to record the daily consumption of the study products, use of any unauthorised products, and use of bisacodyl as well as any other concomitant treatment.

The primary end point was the change in stool frequency from baseline (the week before randomization) to after 3 weeks of product consumption. Secondary end points were the rate of success (defined as 3 or more bowel movements per week and <1 faecal incontinence episode in 2 weeks over the last 2 weeks of product consumption) and the rate of responders (with a responder defined as a subject who reports a stool frequency ≥3 episodes during the last week of product consumption). Other secondary end points were calculated over the 3-week product consumption period: stool frequency; stool consistency; frequency of episodes of faecal incontinence; frequency of pain during defecation; frequency of digestive symptoms (abdominal pain and flatulence); frequency of adverse effects (nausea, diarrhea, and bad taste); and frequency of intake of bisacodyl.

Data collection was done by local physicians who completed case record forms. Independent clinical research associates visited the recruiting sites to monitor all patients’ data. Adverse events were monitored by the research associates. After completing the study, but before any analysis or unblinding, 3 authors (Miss Roseboom, Dr Chmielewska, and Dr Tabbers) checked all primary and secondary end points with primary source data. Before any analysis and without knowledge of product allocation, the study group judged all exclusions, serious adverse events, and end points not fully specified in the protocol in individual patients. After agreement, analyses were done with blinding of the given products preserved. After revealing the results of the blinded analyses to the study group, the randomization code was broken on October 26, 2009.

**Statistical Analysis**

Descriptive statistics were performed for baseline characteristics. Continuous variables were described by means and SD, or in the case of skewed distributions, by medians and 25th and 75th percentiles. Categorical variables...
were described by percentages. Almost all clinical outcomes were assessed 3 times during the intervention period, which led to the following statistical approach. For continuous outcomes, linear mixed models were made containing time (3 levels), product, and the interaction between time and product, and the value of the outcome at baseline. On the basis of the linear mixed model, we performed an overall test for difference in outcome between product groups across all time points and assessed the difference with 95% confidence interval at the third week of product consumption. In case of a binary outcome, a generalized estimating equation logistic regression was made to take the correlated structure of the data into account. All analyses were done on the intention-to-treat population. All statistical tests were performed with a 2-sided significance level of 5%. All analyses were done with SPSS 16.0 (SPSS Inc, Chicago, IL). The statistical analysis of the entire data sets pertaining to efficacy (specifically primary and major secondary efficacy end points) and safety (specifically serious adverse events as defined in federal guidelines) have been independently confirmed by a biostatistician who is not employed by the corporate entity.

The sample size was based on the percentage of success in both groups. In the intervention group (fermented milk containing *B. lactis* DN-173 010, toilet training, bowel diary) we expected this proportion to be $\sim 35\%$, and in the control group (acidified milk without ferments, toilet training, bowel diary) to be $\sim 15\%$. The choice of 15% was justified by a previous study by van der Plas et al in which it was shown that 15% of children with untreated chronic defecation problems were helped by an approach of toilet training and completing a daily bowel diary. To demonstrate such a difference, it required a total sample size of 146 using a 2-sided significance ($\alpha$) level of 0.05 and a power ($\beta$) of 80%. To allow for loss because of withdrawal, a total number of 160 subjects were randomly assigned.

**RESULTS**

Between February 2008 and November 2008, 186 children were assessed for eligibility of whom 26 could not be included (Fig 2). A total of 160 children were correctly randomized to consume either the fermented dairy product ($n = 79$) or the control ($n = 80$) (Fig 2). Eleven children were lost to follow-up without having any outcome data during follow-up. These 11 patients, 5 in the probiotic group and 6 in the control group, were excluded from the final analysis. In Table 1 the baseline characteristics are shown.

The mean stool frequency was 1.6 episodes per week at baseline in the probiotic group and 4.5 at week 3 compared with 1.3 episodes per week at baseline in the control group and 3.9 at week 3. The increase in stool frequency from baseline to end of study (primary
end point) was therefore 2.9 ± 3.2 in probiotic group versus 2.6 ± 2.6 in control group. This difference was not statistically significant (P = .35) (Fig 3). The mean difference for the primary end point between the probiotic and control group was 0.47 (95% confidence interval [CI]: 0.52 to 1.45). The test for a difference in stool frequency over 3 weeks was not statistically significant (P = .51) (Fig 3).

The rate of success was 38% (27/71) in the probiotic group versus 24% (17/72) in the control group, with a risk difference of 14% (95% CI: −1% to 29%, P = .06). The rate of responders was 72% (51/71) in the probiotic group versus 64% (46/72) in the control group, corresponding with a difference of 8% (95% CI: −7.3% to 23%, P = .31).

Stool consistency was not statistically significantly different between the probiotic group and the control group (mean score of 3.3 in the probiotic group versus 3.5 in the control group at week 3, P = .07 over 3 weeks). The test for difference in the proportion of patients with episodes of faecal incontinence revealed a P value of .19. The overall test for difference in pain during defecation revealed no statistically significant difference (P = .14), nor did the test for difference in abdominal pain (P = .92). Flatulence was reported less frequently in the probiotic group compared with the control group, with a difference of 13% at week 1, 24% at week 2, and 11% at week 3. The overall difference in flatulence over 3 weeks revealed a significantly difference between groups in favor of the probiotic group (P = .02). The overall test for difference of bisacodyl intake revealed a P value of .12. In Table 2 the overall test for differences during product consumption period and specific differences for all outcomes at week 3 is shown.

### Adverse Events and Safety
Two serious adverse events occurred during this study, probably not related to consumption of the study products:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>P for Overall Differences</th>
<th>P (GEE)</th>
<th>Probiotic</th>
<th>Control</th>
<th>Probiotic %</th>
<th>Control %</th>
<th>Difference (95% CI)</th>
<th>Estimated Odds Ratio (95% CI): Product vs Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in stool frequency</td>
<td>.35</td>
<td>2.9</td>
<td>2.6</td>
<td></td>
<td></td>
<td></td>
<td>0.3 (−1.45−0.51)</td>
<td></td>
</tr>
<tr>
<td>Mean stool frequency</td>
<td>.51</td>
<td>4.5</td>
<td>3.9</td>
<td></td>
<td></td>
<td></td>
<td>0.6 (−0.60−1.20)</td>
<td></td>
</tr>
<tr>
<td>Mean stool consistency</td>
<td>.07</td>
<td>3.3</td>
<td>3.3</td>
<td></td>
<td></td>
<td></td>
<td>−0.2 (−0.64−0.03)</td>
<td></td>
</tr>
<tr>
<td>Rate of success</td>
<td>.06</td>
<td>38</td>
<td>24</td>
<td></td>
<td></td>
<td></td>
<td>14 (−1−29%)</td>
<td></td>
</tr>
<tr>
<td>Rate of responders</td>
<td>.31</td>
<td>72</td>
<td>64</td>
<td></td>
<td></td>
<td></td>
<td>8 (−7.3−23%)</td>
<td></td>
</tr>
<tr>
<td>Faecal incontinence</td>
<td>.18</td>
<td>36.6</td>
<td>48.6</td>
<td></td>
<td></td>
<td></td>
<td>1.48 (0.83−2.64)</td>
<td></td>
</tr>
<tr>
<td>Pain during defecation</td>
<td>.14</td>
<td>48.6</td>
<td>41.4</td>
<td></td>
<td></td>
<td></td>
<td>0.67 (0.35−1.15)</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>.92</td>
<td>58.3</td>
<td>54.2</td>
<td></td>
<td></td>
<td></td>
<td>0.97 (0.56−1.69)</td>
<td></td>
</tr>
<tr>
<td>Flatulence</td>
<td>.02</td>
<td>23.6</td>
<td>34.7</td>
<td></td>
<td></td>
<td></td>
<td>0.48 (0.28−0.89)</td>
<td></td>
</tr>
<tr>
<td>Use of bisacodyl</td>
<td>.12</td>
<td>23.6</td>
<td>30.6</td>
<td></td>
<td></td>
<td></td>
<td>0.61 (0.32−1.13)</td>
<td></td>
</tr>
</tbody>
</table>

GEE indicates generalized estimating equation.
n 1 child broke his arm, and 1 developed gynecological pain, which was caused by a gynecological cyst. Other adverse events that might related to consumption of the study products were gastrointestinal enteritis (intervention group, n = 1; control group, n = 3), nausea/vomiting (intervention group, n = 3; control group, n = 2), and Candida-infection of the anorectal region (control group, n = 1).

DISCUSSION

This randomized, double-blind controlled trial in constipated children with a defecation frequency of <3 episodes per week revealed no significant difference in the increase in stool frequency with the fermented dairy product that contains B lactis strain DN-173 010 and the control group. Across all other clinical outcomes, differences in general were in favor of probiotics (Table 2). These differences were small and not statistically significant with the exception of flatulence. No serious adverse events were reported.

This is the first, large, randomized, double-blind controlled trial conducted in constipated children in which the efficacy and safety of a specific probiotic product are investigated. In a recent systematic review of the effects of laxative treatment and dietary measures in the management of childhood constipation, only 2 randomized controlled trials were found in which the effects of probiotics were evaluated.4 In the first small study, 45 children younger than 10 years with chronic constipation were randomly assigned to receive magnesium oxide (50 mg/kg per day [n = 18]) or 8 × 108 CFU per day of the probiotic Lactobacillus casei rhamnosus (n = 18) or placebo (n = 9) twice daily for 4 weeks.14 No statistically significant difference in the defecation frequency was found. However, patients who received either the probiotic strain or the oral laxative had a significantly higher defecation frequency compared with the placebo group (defecation frequency of 0.57 ± 0.17 and 0.55 ± 0.13 times per day, respectively, compared with 0.37 ± 0.10, P = .03). The second trial was conducted to determine if Lactobacillus rhamnosus GG (LGG) is an effective adjunct to lactulose for treating constipation in children. In the trial, 48 children with constipation received 1 mL/kg per day of 70% lactulose plus 10⁹ CFU of LGG or 1 mL/kg per day of 70% lactulose plus placebo, twice daily for 12 weeks.15 There were no significant differences in rates of product success (defined as ≥3 spontaneous stools per week with no faecal incontinence) at 12 and 24 weeks between the LGG group (rates: 72% and 64%, respectively) and the placebo group (rates: 68% and 65%, respectively). In neither trial were any adverse events reported.

In contrast with our study, in recent studies in adults it has been shown that the same fermented dairy product that contains B lactis DN-173 010 significantly reduced colonic transit times in young and elderly healthy adults16–20 and in constipation-predominant IBS patients.21 Moreover, a randomized, double-blind, controlled trial performed in IBS patients with constipation revealed a significant increase compared with controls, in stool frequency over the 6 weeks of product consumption in the subgroup of patients with a defecation frequency of <3 episodes per week,9 and another clinical study performed in constipated women with a defecation frequency <3 episodes per week revealed the same result after 2 weeks of product consumption.9 The difference in efficacy of the fermented dairy product that contains B lactis DN-173 010 between adults and children underscores the hypothesis that constipation in children differs considerably from that in constipated adults with regard to its prevalence, onset, etiology, symptoms, treatment, and prognosis.22

We found in the control group a higher rate of success than expected, namely 24% instead of 15%. In an earlier study by Nurko et al23 conducted in children with functional constipation, a response rate of 40% was found in the placebo group. The authors suggested a significant role of behavior modification, including toilet training and parental positive reinforcement, in determining the high placebo response rate. In our study, toilet training in combination with keeping a bowel diary in addition with the consumption of a product could also have played an important role in achieving this high success rate in the control group. On the other hand, it could be because of a true placebo effect. This effect could be caused by the high level of expectancy of children and their parents participating in this study and the frequent contacts between the doctors and patients. However, this high placebo success rate must challenge clinical researchers to evaluate the effect of placebo compared with new compounds emerging for the treatment of childhood constipation.

The success rate, however, is higher in the probiotic group, namely 38% vs 24% in the control group. The difference of 14% between both groups could be explained by coincidence. Although this difference is not statistically significant, an increase in dosage of the probiotics or a longer consumption period might result in a significant difference in favor of probiotics. In addition, despite the absence of statistical difference in laxative intake with binary analysis, the higher intake of laxatives observed in the control group compared with probiotic group could partially explain the absence of signif-
significant difference between the 2 groups on stool frequency. Indeed, quantitative posthoc analysis of the mean number of bisacodyl intake per week and per group showed a higher intake of bisacodyl in the control group (0.59 vs 0.35 for the probiotic group, *P* = .0069).

This study has some limitations that could have caused bias. Firstly, it is unknown whether the control product may also have had a laxative effect. However, it has been formulated to be as neutral as possible regarding a potential benefit on constipation. Three studies in which the same control product was used did not reveal such an effect in constipated women (Yang et al), in IBS with constipation (Agrawal et al), and in the general population (Guyonnet et al). All children received 3 enemas before consuming the products, and so the effect of the treatment product was tested in altered conditions, already associated with toilet training and use of enemas. Thus, it could be fruitful to wait for a longer period to observe the disappearance of the enema effect and a potential statistically significant difference in stool frequency between groups. Secondly, a specific diet questionnaire that evaluated the child’s daily intake was not included in this study. Therefore, dietary influences on bowel patterns in the 2 different countries could not be ruled out. To our knowledge, however, there is not much difference in the general diet between Poland and the Netherlands. More importantly, a recent systematic review reported that data are lacking that reveals that increasing fiber intake has a beneficial effect in constipated children. Thirdly, this study was conducted in secondary and tertiary centers, which have attracted more severely constipated children. Future studies in primary care settings should be conducted to confirm or repudiate these data. A final limitation could be the effect of loss-to follow-up, although this percentage was comparable in both groups.

**CONCLUSION**

The product that contains *B. lactis* strain DN-173 010 did increase stool frequency in constipated children, but the increase was comparable in the control group. There is currently not sufficient evidence to support a general recommendation about the use of probiotics in the treatment of functional childhood constipation. Future studies should focus on whether the consumption of this probiotic product could be more effective in children with a short history of constipation.

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Investigators comprise, in Poland, The Medical University of Warsaw, H. Sza-jewska; and in the Netherlands, Emma Children’s Hospital/Academic Medical Centre Amsterdam, M.A. Benninga; University Hospital Groningen, E. Rings; Amphia Hospital Breda, S. De Pont; Antonius Hospital Nieuwegein, A. Vlieger; Isala Hospital Zwolle, O. Norbruis; Zuwe Hofpoort Hospital Woerden, W. Verwijs; Academic Hospital Rotterdam, M.Y. Berger; Medical Centre Alkmaar, E.K. George; Gelderse Vallei Hospital Ede, G.J. van der Burg; Spaarne Hospital Hoofddorp, J. Bokma; Catharina Hospital Eindhoven, N. A.J. de la Haye, R. Pel-leboer, and B. G. Werrij; Flevo Hospital Almere, M. Trijbeils-Smulders; and Rijnstate Hospital Arnhem, E. Leijn.

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Fermented Milk Containing *Bifidobacterium lactis* DN-173 010 in Childhood Constipation: A Randomized, Double-Blind, Controlled Trial

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