EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2014. Scientific Opinion on the substantiation of a health claim related to a combination of Bifidobacterium longum LA 101, Lactobacillus helveticus LA 102, Lactococcus lactis LA 103 and Streptococcus thermophilus LA 104 and reducing intestinal discomfort pursuant to Article 13(5) of Regulation (EC) No 1924/2006

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SCIENTIFIC OPINION

Scientific Opinion on the substantiation of a health claim related to a combination of *Bifidobacterium longum* LA 101, *Lactobacillus helveticus* LA 102, *Lactococcus lactis* LA 103 and *Streptococcus thermophilus* LA 104 and reducing intestinal discomfort pursuant to Article 13(5) of Regulation (EC) No 1924/2006[1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2,3]

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

Following an application from PiLeJe, submitted pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of France, the Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to a combination of *Bifidobacterium longum* LA 101, *Lactobacillus helveticus* LA 102, Lactococcus *lactis* LA 103 and *Streptococcus thermophilus* LA 104 and reducing intestinal discomfort. The food that is the subject of the health claim is a combination of four bacterial strains—*B. longum* LA 101, *L. helveticus* LA 102, *L. lactis* LA 103 and *S. thermophilus* LA 104. The Panel considers that the food, a combination of *B. longum* LA 101, *L. helveticus* LA 102, *L. lactis* LA 103 and *S. thermophilus* LA 104, which is the subject of the health claim is sufficiently characterised. The claimed effect proposed by the applicant is "improves intestinal comfort". The Panel considers that reduction of gastro-intestinal discomfort is a beneficial physiological effect. The Panel considers that the only human study provided for the substantiation of the claim (with limitations) did not find an effect of a combination of the bacterial strains being the subject of the claim on gastrointestinal discomfort. The Panel concludes that a cause and effect relationship has not been established between the consumption of a combination of *B. longum* LA 101, *L. helveticus* LA 102, *L. lactis* LA 103 and *S. thermophilus* LA 104 and reducing gastro-intestinal discomfort.

KEY WORDS

Bifidobacterium longum LA 101, *Lactobacillus helveticus* LA 102, *Lactococcus lactis* LA 103, *Streptococcus thermophilus* LA 104, intestinal discomfort, health claims

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[1] On request from the Competent Authority of France following an application by PiLeJe, Question No EFSA-Q-2013-00892, adopted on 10 April 2014.

[2] Panel members: Carlo Agostoni, Roberto Berni Canani, Susan Fairweather-Tait, Marina Heinonen, Hannu Korhonen, Sébastien La Vieille, Rosangela Marchelli, Ambroise Martin, Androniki Naska, Monika Neuhäuser-Berthold, Grażyna Nowicka, Yolanda Sanz, Alfonso Siani, Anders Sjödin, Martin Stern, Sean (J.J.) Strain, Inge Tetens, Daniel Tomé, Dominique Turck and Hans Verhagen. Correspondence: nda@efsa.europa.eu

[3] Acknowledgement: The Panel wishes to thank the members of the Working Group on Claims: Carlo Agostoni, Jean-Louis Bresson, Susan Fairweather-Tait, Marina Heinonen, Ambroise Martin, Hildegard Przyrembel, Yolanda Sanz, Alfonso Siani, Anders Sjödin, Sean (J.J.) Strain, Inge Tetens, Hendrik van Loveren, Hans Verhagen and Peter Willatts for the preparatory work on this scientific opinion.

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SUMMARY

Following an application from PiLeJe, submitted pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of France, the Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to a combination of Bifidobacterium longum LA 101, Lactobacillus helveticus LA 102, Lactococcus lactis LA 103 and Streptococcus thermophilus LA 104 and reducing intestinal discomfort.

The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence. The application includes a request for the protection of proprietary data.

The food that is the subject of the health claim is a combination of B. longum LA 101, L. helveticus LA 102, L. lactis LA 103 and S. thermophilus LA 104. The Panel considers that the food, a combination of B. longum LA 101, L. helveticus LA 102, L. lactis LA 103 and S. thermophilus LA 104, is sufficiently characterised.

The claimed effect proposed by the applicant is "improves intestinal comfort". The target population proposed by the applicant is people characterised by a digestive discomfort such as bloating and flatulence and change in stool frequency. The Panel considers that reduction of gastro-intestinal discomfort is a beneficial physiological effect.

For the scientific substantiation of the claim, the applicant provided the results of one published human study and one in vitro study. The Panel considers that the only human study provided (with methodological limitations) did not find an effect of a combination of the bacterial strains being the subject of the claim on reducing gastrointestinal discomfort. The Panel considers that the in vitro study evaluating survival of the four bacterial strains that are the subject of the claim in an artificial gastro-intestinal model does not provide data that can be used for the substantiation of a claim related to gastro-intestinal discomfort.

On the basis of the data presented, the Panel concludes that a cause and effect relationship has not been established between the consumption of a combination of B. longum LA 101, L. helveticus LA 102, L. lactis LA 103 and S. thermophilus LA 104 and reducing intestinal discomfort.

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BACKGROUND

Regulation (EC) No 1924/2006[4] harmonises the provisions that relate to nutrition and health claims, and establishes rules governing the Community authorisation of health claims made on foods. As a rule, health claims are prohibited unless they comply with the general and specific requirements of this Regulation, are authorised in accordance with this Regulation, and are included in the lists of authorised claims provided for in Articles 13 and 14 thereof. In particular, Article 13(5) of this Regulation lays down provisions for the addition of claims (other than those referring to the reduction of disease risk and to children's development and health) which are based on newly developed scientific evidence, or which include a request for the protection of proprietary data, to the Community list of permitted claims referred to in Article 13(3).

According to Article 18 of this Regulation, an application for inclusion in the Community list of permitted claims referred to in Article 13(3) shall be submitted by the applicant to the national competent authority of a Member State, which will make the application and any supplementary information supplied by the applicant available to the European Food Safety Authority (EFSA).

STEPS TAKEN BY EFSA

- The application was received on 11/11/2013.
- The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence.
- The scientific evaluation procedure started on 4/12/2013.
- On 22/01/2014, the Working Group on Claims of the NDA Panel agreed on a list of questions for the applicant to provide additional information to accompany the application. The clock was stopped on 29/01/2014 and restarted on 05/02/2014, in compliance with Article 18(3) of Regulation (EC) No 1924/2006.
- On 05/02/2014, EFSA received the requested information (which was made available to EFSA in electronic format on 04/02/2014).
- During its meeting on 10/04/2014, the NDA Panel, having evaluated the data submitted, adopted an opinion on the scientific substantiation of a health claim related to a combination of *B. longum* LA 101, *L. helveticus* LA 102, *L. lactis* LA 103 and *S. thermophilus* LA 104 and reducing intestinal discomfort.

TERMS OF REFERENCE

EFSA is requested to evaluate the scientific data submitted by the applicant in accordance with Article 16(3) of Regulation (EC) No 1924/2006. On the basis of that evaluation, EFSA will issue an opinion on the scientific substantiation of a health claim related to a combination of *B. longum* LA 101, *L. helveticus* LA 102, *L. lactis* LA 103 and *S. thermophilus* LA 104 and reducing intestinal discomfort.

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation for the marketing of a combination of *B. longum* LA 101, *L. helveticus* LA 102, *L. lactis* LA 103 and *S. thermophilus* LA 104, a positive assessment of its safety, *nor a decision on whether* a combination of *B. longum* LA 101, *L. helveticus* LA 102, *L. lactis* LA 103 and *S. thermophilus* LA 104 is, or is not, classified as a foodstuff. It should be noted that such an assessment is not foreseen in the framework of Regulation (EC) No 1924/2006.

[4] Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. OJ L 404, 30.12.2006, p. 9–25.

It should also be highlighted that the scope, the proposed wording of the claim, and the conditions of use as proposed by the applicant may be subject to changes, pending the outcome of the authorisation procedure foreseen in Article 18(4) of Regulation (EC) No 1924/2006.

INFORMATION PROVIDED BY THE APPLICANT

Applicant's name and address: PiLeJe, 37 Quai de Grenelle, 75738 Paris Cedex 15, France.

The application includes a request for the protection of proprietary data in accordance with Article 21 of Regulation (EC) No 1924/2006 (Drouault-Holowacz et al., 2008).

Food/constituent as stated by the applicant

According to the applicant, the food for which a health claim is made is a combination of four bacterial strains—*Bifidobacterium longum* LA 101 (29 %), *Lactobacillus helveticus* LA 102 (29 %), *Lactococcus lactis* LA 103 (29 %) and *Streptococcus thermophilus* LA 104 (13 %)—mixed with excipients as mentioned below: potato starch (Perfectamyl D6) (quantity per 2.5 g sachet—1.956 g), dextrose (ROFEROSE® ST) (0.25 g), maltodextrin (GLUCIDEX®) (0.03 g), chicory fructo-oligosaccharides (Beneo®P95), mix of four probiotic strains (0.114 g) and cellulose (Avicell® PH) (0.025 g).

Health relationship as claimed by the applicant

According to the applicant, the claimed effect is "improves intestinal comfort".

Wording of the health claim as proposed by the applicant

The applicant has proposed the following wording for the health claim: "improves intestinal comfort", "helps to alleviate/decrease intestinal discomfort", "helps to alleviate/reduces bloating" and "helps to alleviate/reduces flatulence".

Specific conditions of use as proposed by the applicant

The applicant has proposed an intake of one sachet (2.5 g) per day for 28 days. Each sachet has to be taken once daily in the fasting state, at least 3 hours after a meal and 15 minutes before the next meal. The powder has to be dissolved in water 10 minutes before its ingestion. The target population is people characterised by a digestive discomfort such as bloating and flatulence and change in stool frequency.

ASSESSMENT

1. Characterisation of the food

The food that is the subject of the health claim is a combination of four bacterial strains—*Bifidobacterium longum* LA 101 (29 %), *Lactobacillus helveticus* LA 102 (29 %), *Lactococcus lactis* LA 103 (29 %) and *Streptococcus thermophilus* LA 104 (13 %)—with other food ingredients or excipients: 1.96 g potato starch (Perfectamyl D6), 0.25 g dextrose (ROFEROSE® ST), 0.03 g maltodextrin (GLUCIDEX®), 0.125 g chicory fructo-oligosaccharides (Beneo®P95) and 0.025 g cellulose (Avicell® PH). The concentration of the bacterial strains in colony-forming units (CFU) is 10^{10} CFU per sachet (2.9×10^9 CFU *B. longum* LA 101; 2.9×10^9 CFU *L. helveticus* LA 102; 2.9×10^9 CFU *L. lactis* LA 103; 1.3×10^9 CFU *S. thermophilus* LA 104).

Data related to microbiological safety and stability of the strains were provided.

The strain *B. longum* LA 101 (also named R0175) was deposited in the Collection Nationale de Cultures de Microorganismes (CNCM) under the deposit number I-3470. The CNCM is a restricted-access non-public collection which has the status of International Depositary Authority under the Budapest Treaty. Data on phenotypic (morphology, fermentation pattern, biochemical tests) and genotypic characterisation of the strain, including species-specific polymerase chain reaction (PCR) and 16S rRNA gene and *tuf* gene sequence analyses for species identification, and pulsed-field gel

electrophoresis (PFGE) for strain typing, were provided. The Panel considers that the strain *B. longum* LA 101 is sufficiently characterised.

The strain *L. helveticus* LA 102 (also named R0052) was deposited in the CNCM under the deposit number I-1722. Data on phenotypic (morphology, fermentation pattern, enzymatic activities, 2D-protein analysis) and genotypic characterisation of the strain, including 16S rRNA gene and 16S–23S rRNA intergenic region sequence analyses, DNA–DNA hybridisation and amplified ribosomal DNA restriction analysis (ARDRA) for species identification, and PFGE for strain typing, were provided. According to the applicant, this strain was initially identified as *L. acidophilus*, but more recently re-classified as *L. helveticus*. The Panel considers that the strain *L. helveticus* LA 102 is sufficiently characterised.

The strain *L. lactis* LA 103 (also named R1058) was deposited in the CNCM under the deposit number MA 67/4J. Data on phenotypic (morphology, fermentation pattern, biochemical tests) and genotypic characterisation of the strain, including 16S rRNA gene sequence analysis for species identification and multi-locus sequence typing (MLST), randomly amplified polymorphic DNA (RAPD) and PFGE analyses for strain typing, were provided. The Panel considers that the strain *L. lactis* LA 103 is sufficiently characterised.

The strain *S. thermophilus* LA 104 (also named R1018) was characterised phenotypically (morphology, fermentation pattern, biochemical tests) and genotypically, including 16S rRNA gene sequence analysis for species identification and PFGE for strain typing. The strain was deposited in the CNCM with the number CNCM-I4691. The Panel considers that the strain *S. thermophilus* LA 104 is sufficiently characterised.

The Panel considers that the food, a combination of *B. longum* LA 101, *L. helveticus* LA 102, *L. lactis* LA 103 and *S. thermophilus* LA 104, which is the subject of the health claim is sufficiently characterised.

2. Relevance of the claimed effect to human health

The claimed effect proposed by the applicant is "improves intestinal comfort". The target population proposed by the applicant is people characterised by a digestive discomfort such as bloating and flatulence and change in stool frequency.

The Panel considers that reduction of gastrointestinal discomfort is a beneficial physiological effect.

3. Scientific substantiation of the claimed effect

The applicant performed a literature search in the PubMed database. The following search terms were used: "probiotic", "probiotics", "Lactibiane", "probiotic/ibs", "probiotics/ibs", "probiotic/transit", "probiotics/transit". A manual search was also performed.

The applicant identified one published human study (Drouault-Holowacz et al., 2008, claimed as proprietary) and one *in vitro* study (Denis et al., unpublished) as pertinent to the claim.

A placebo-controlled, randomised, double-blind, multi-centre, parallel study by Drouault-Holowacz et al. (2008) investigated the effects of daily consumption of the combination of bacterial strains which is the subject of the claim on symptoms related to gastro-intestinal discomfort. The study was performed in a group of 116 outpatients with irritable bowel syndrome (IBS) according to the Rome II criteria and a discomfort/pain score superior or equal to 1 assessed using a 0–3 Likert scale. The combination of four bacterial strains which is the subject of the claim, was provided in the form of 2.5 g sachet taken once daily or placebo (of identical appearance and identical composition except for the bacterial strains) and was given randomly for four weeks. A questionnaire assessing intensity of symptoms was completed by the subjects each week. The primary outcome was "satisfactory relief" of overall IBS symptoms measured weekly by a binary scale answer (Yes/No) to a question about satisfactory relief

of IBS symptoms as reported in a previous study (Kellow et al., 2003). The subjects also had to answer a second question related to the relief of symptoms of abdominal discomfort/pain using a scale with five different severity descriptors in accordance with Müller-Lissner et al. (2001). It was unclear to the Panel whether answers to both questions were used to determine the primary outcome (and how results were combined) or if the second question was used only to determine the secondary outcome (abdominal pain). Upon a request by EFSA, the applicant indicated that both questions were used for the assessment of the primary outcome, defined as "satisfactory relief" of overall IBS symptoms, and that relief of pain was treated as a secondary outcome. Other secondary endpoints included weekly assessment of discomfort/pain, intensity of abdominal pain using a 10 cm visual analogue scale (0, not at all; 10, acute, unimaginable) and self-assessment of stool frequency and consistency. Additionally, subjects completed the IBS specific FDD-QoL (Functional Digestive Disorders Quality-of-Life) questionnaire and health status Short Form-36 (SF-36) questionnaire at baseline and at the end of the treatment.

The study was adequately powered in relation to primary outcomes. A total of 100 subjects finished the study (76 women, mean age 46 years, 48 in the study group and 52 in control group). The reasons for drop-outs (one in the placebo group and five in the test group) were given. Characteristics of subjects of both groups were reported to be comparable at baseline regarding discomfort/pain score.

In statistical analysis of the results, the differences in items from questionnaires between the two intervention groups were analysed applying the two-sided chi^2-test or Fisher exact test, as appropriate. Answers on visual analogue scales were measured in centimetres and compared (row values and changes expressed in percentages) between groups by the Mann–Whitney test and within groups (week 5 and week 1) by Wilcoxon's rank-sum test. The percentage of variation were calculated using the formula ([Wk4 –Wk0]/Wk0) × 100. The Panel notes that correction for multiple comparisons was not taken into account in the statistical analyses. In the study report, the results were presented as both per protocol (PP) (100 subjects) and intention to treat (ITT) (106 subjects) analyses.

The study reported that the combination of bacterial strains had no effect on the primary outcome, "relieving symptoms of IBS", compared with placebo (42.6 % of subjects with improvement vs. 42.3 % subjects with improvement in per protocol analysis, and 37.7 % vs. 42.7 % in ITT analysis). The differences in relation to relief of symptoms of abdominal discomfort/pain with the use of five scale questionnaires were not statistically significant for each of five time points measured for both PP and ITT analyses. The differences in the intensity of pain/discomfort on the visual analogue scale, stool frequency and consistency, SF-36 and FDD-QoL were also not statistically significant. Significant differences were reported for some components of the questionnaires only and in certain subgroups of subjects and were inconsistent at different time points. The Panel notes that results of these secondary analyses were inconsistent.

The Panel notes also that only two of the questionnaires used in the study were validated (SF-36 and FDD-QoL), while other questionnaires/scales were previously used in other studies. Upon a request by EFSA regarding the validation of questionnaires/scales, the applicant indicated that "they employed definitions of clinically meaningful improvement in IBS as a patient response (yes or not) of satisfactory relief of overall IBS symptoms or abdominal pain and discomfort (Irvine et al., 2006) and that these definitions are assumed to have faced validation". The Panel notes that the previous use of a questionnaire/scale is not necessarily a proof of validity and that the applicant has not provided specific evidence of the validation of the questionnaires used.

The Panel considers that this study (with some methodological limitations) did not show an effect of a combination of bacterial strains, which is the subject of the claim, on gastro-intestinal discomfort.

In the second study provided, the survival of the four bacterial strains, a combination of which is the subject of the claim, was evaluated in an artificial gastro-intestinal model (TIM) (Denis et al., unpublished). The Panel considers that this study does not provide data that can be used for the substantiation of a claim related to gastro-intestinal discomfort.

In weighing the evidence, the Panel considers that the only human study (with methodological limitations) provided for the substantiation of the claim did not show an effect of a combination of the bacterial strains, which is the subject of the claim, on reducing gastro-intestinal discomfort.

The Panel concludes that a cause and effect relationship has not been established between the consumption of a combination of *Bifidobacterium longum* LA 101, *Lactobacillus helveticus* LA 102, *Lactococcus lactis* LA 103 and *Streptococcus thermophilus* LA 104 and reducing gastro-intestinal discomfort.

CONCLUSIONS

On the basis of the data presented, the Panel concludes that:

- The food, a combination of *Bifidobacterium longum* LA 101, *Lactobacillus helveticus* LA 102, *Lactococcus lactis* LA 103 and *Streptococcus thermophilus* LA 104, which is the subject of the health claim, is sufficiently characterised.
- The claimed effect is "improves intestinal comfort". The target population proposed by the applicant is people characterised by a digestive discomfort such as bloating and flatulence and change in stool frequency. The Panel considers that reduction of gastro-intestinal discomfort is a beneficial physiological effect.
- A cause and effect relationship has not been established between the consumption of a combination of *Bifidobacterium longum* LA 101, *Lactobacillus helveticus* LA 102, *Lactococcus lactis* LA 103 and *Streptococcus thermophilus* LA 104 and reducing gastro-intestinal discomfort.

DOCUMENTATION PROVIDED TO EFSA

Health claim application on a combination of *Bifidobacterium longum* LA 101, *Lactobacillus helveticus* LA 102, *Lactococcus lactis* LA 103 and *Streptococcus thermophilus* LA 104 and reducing intestinal discomfort pursuant to Article 13(5) of Regulation (EC) No 1924/2006 (Claim serial No: 0401_FR). November 2013. Submitted by PiLeJe.

REFERENCES

Denis S, Alric M, Holowacz S, Martin F, Rousseau V and Paul F, unpublished. Collaboration de Recherche No ERT 03/01 (suite de la collaboration No ERT02/02, Rapport final).

Drouault-Holowacz S, Bieuvelet S, Burckel A, Cazaubiel M, Dray X and Marteau P, 2008. A double blind randomized controlled trial of a probiotic combination in 100 patients with irritable bowel syndrome. Gastroentérologie Clinique et Biologique, 32, 147–152.

Irvine EJ, Whitehead WE, Chey WD, Matsueda K, Shaw M, Talley NJ, Veldhuyzen van Zanten SJ and Design of Treatment Trials Committee, 2006. Design of treatment trials for functional gastrointestinal disorders. Gastroenterology, 130, 1538–1551.

Kellow J, Lee OY, Chang FY, Thongsawat S, Mazlam MZ, Yuen H, Gwee KA, Bak YT, Jones J and Wagner A, 2003. An Asia-Pacific, double blind, placebo controlled randomised study to evaluate the efficacy, safety, and tolerability of tegaserod in patients with irritable bowel syndrome. Gut, 52, 671–676.

Müller-Lissner SA, Fumagalli I, Bardhan KD, Pace F, Pecher E, Nault B and Ruegg P, 2001. Tegaserod, a 5-HT4 receptor partial agonist, relieves symptoms in irritable bowel syndrome patients with abdominal pain, bloating and constipation. Alimentary Pharmacology and Therapeutics, 15, 1655–1666.

ABBREVIATIONS

ARDRA	amplified ribosomal DNA restriction analysis
CFU	colony-forming unit
CNCM	Collection Nationale de Cultures de Microorganismes
DNA	deoxyribonucleic acid
FDD	Functional Digestive Disorders
IBS	irritable bowel syndrome
ITT	intention to treat
MLST	multi-locus sequence typing
PCR	polymerase chain reaction
PFGE	pulsed-field gel electrophoresis
PP	per protocol
RAPD	randomly amplified polymorphic DNA
RNA	ribonucleic acid
SF-36	Short Form-36
TIM	polyfermentor intestinal model