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SCIENTIFIC OPINION

Scientific Opinion on the substantiation of a health claim related to Bimuno[®] GOS and reducing gastro-intestinal discomfort pursuant to Article 13(5) of Regulation (EC) No 1924/2006¹

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)^{2,3}

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

Following an application from Clasado Ltd., submitted pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of the United Kingdom, the Panel on Dietetic Products, Nutrition and Allergies was asked to deliver an opinion on the scientific substantiation of a health claim related to Bimuno[®] GOS and reducing gastro-intestinal discomfort. The food constituent that is the subject of the health claim, Bimuno[®] GOS, is sufficiently characterised. The claimed effect is reduction of gastro-intestinal discomfort, which is a beneficial physiological effect. The applicant identified eight human intervention studies, two human observational studies, and three non-human studies as being pertinent to the health claim. The Panel considers that owing to important methodological limitations, no conclusions with respect to the scientific substantiation of the claim can be drawn from the two human intervention studies which investigated the effect of Bimuno[®] GOS on symptoms related to gastro-intestinal discomfort. The remaining human studies, and the animal and *in vitro* studies, addressed the effects of either Bimuno[®] GOS or other galacto-oligosaccharides from a variety of sources on the gut microbiota. The Panel considers that the evidence provided does not establish that an effect of Bimuno[®] GOS on bifidobacteria *per se* is sufficient to predict an effect of Bimuno[®] GOS on gastro-intestinal discomfort *in vivo* in humans. The Panel considers that no human studies have been provided from which conclusions can be drawn for the scientific substantiation of the claim. The Panel concludes that a cause and effect relationship has not been established between the consumption of Bimuno[®] GOS and reducing gastro-intestinal discomfort.

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KEY WORDS

Bimuno[®], GOS, β -galacto-oligosaccharides, gastro-intestinal discomfort, health claims

¹ On request from the Competent Authority of the United Kingdom following an application by Clasado Ltd., Question No EFSA-Q-2011-00401, adopted on 24 November 2011.

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SUMMARY

Following an application from Clasado Ltd., submitted pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of the United Kingdom, the Panel on Dietetic Products, Nutrition and Allergies was asked to deliver an opinion on the scientific substantiation of a health claim related to Bimuno[®] GOS and reducing gastro-intestinal discomfort.

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

The food constituent that is the subject of the health claim is Bimuno[®] GOS, a mixture of β -galactooligosaccharides which is produced through conversion of lactose by enzymes from *Bifidobacterium bifidum* NCIMB 41171. The Panel considers that Bimuno[®] GOS is sufficiently characterised.

The claimed effect is “reduce bloating, flatulence and intestinal pain, that can be described collectively as intestinal discomfort”. The target population as proposed by the applicant is individuals over 3 years of age. The Panel considers that reducing gastro-intestinal discomfort is a beneficial physiological effect.

The applicant identified eight randomised, controlled, human intervention studies, two human observational studies, and three non-human studies as being pertinent to the health claim.

Three of the human intervention studies provided addressed the effects of Bimuno[®] GOS on symptoms related to gastro-intestinal discomfort. One of these was designed to investigate the effects of Bimuno[®] GOS on the incidence of travellers’ diarrhoea in adults. Upon EFSA’s request, the applicant clarified that this study was provided to indicate that Bimuno[®] GOS is “bifidogenic” and does not present untoward effects. The Panel considers that no conclusions can be drawn from this study for the scientific substantiation of the claim.

A placebo-controlled, randomised, double-blind, cross-over study investigated the effects of daily consumption of Bimuno[®] GOS on symptoms related to gastro-intestinal discomfort. A total of 91 volunteers suffering from gastro-intestinal discomfort were randomised to consume daily 2.75 g of Bimuno[®] (1.37 g of Bimuno[®] GOS; n=45) or 2.75 g maltodextrin (control; n=46) for two weeks each with a two-week washout period in between. Primary outcomes of the study were incidence, duration and severity of bloating (defined as feeling bloated or experiencing abdominal fullness often), occurrence of abdominal pain/discomfort, flatulence, need to defecate, global assessment of relief, and general well being. Secondary outcomes were stool frequency, stool consistency and mood. A total of 83 volunteers completed the study and entered the analysis. The Panel notes the important methodological limitations of this study (e.g. short duration, inappropriate statistical analysis for cross-over designs, and no ITT analysis) and considers that no conclusions can be drawn from this study for the scientific substantiation of the claim.

In a randomised, placebo-controlled intervention study, after a two-week run-in period, 60 subjects with Rome II positive irritable bowel syndrome were randomised into one of the following study arms: a) placebo (7 g/day maltodextrin); b) Bimuno[®] 7 g/day; c) Bimuno[®] 3.5 g/day. All subjects received placebo (maltodextrin) at doses of 3.5 or 7 g/day for four weeks, followed by a two-week “washout” period, and then either placebo (7 g/d maltodextrin) or Bimuno[®] at doses of 3.5 or 7 g/day (containing 1.32 or 2.65 g/day Bimuno[®] GOS, respectively) for four weeks. The primary outcome of the study was changes in the gut bifidobacterial population. Secondary outcomes were bowel movements, stool consistency, bloating, abdominal pain, flatulence, a composite score of symptoms, and anxiety and depression scores, and subjective global assessment of relief. A total of 44 subjects completed the study and entered data analysis. The Panel notes the important methodological limitations of this study (e.g. high dropout rate, multiplicity of outcomes not taken into account in data analysis, statistical methods and results insufficiently described, and no ITT analysis) and

considers that no conclusions can be drawn from this study for the scientific substantiation of the claim.

Human studies, and animal and *in vitro* studies, provided by the applicant addressed the effects of either Bimuno[®] GOS or other galacto-oligosaccharides from a variety of sources on the gut microbiota. The Panel considers that the evidence provided does not establish that an effect of Bimuno[®] GOS on bifidobacteria *per se* is sufficient to predict an effect of Bimuno[®] GOS on gastro-intestinal discomfort *in vivo* in humans.

The Panel considers that no human studies have been provided from which conclusions can be drawn for the scientific substantiation of the claim.

The Panel concludes that a cause and effect relationship has not been established between the consumption of Bimuno[®] GOS and reducing gastro-intestinal discomfort.

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BACKGROUND

Regulation (EC) No 1924/2006⁴ 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 Art 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 12/05/2011.
- The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence and including a request for the protection of proprietary data.
- On 23/05/2011, during the validation process of the application, EFSA sent a request to the applicant to provide missing information.
- The applicant provided the missing information on 09/06/2011.
- The scientific evaluation procedure started on 20/06/2011.
- During its meeting on 13-15 July 2011, 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, and the clock was stopped on 21/07/2011 in compliance with Art. 18(3) of Regulation (EC) No 1924/2006.
- On 03/08/2011, EFSA received the requested information as submitted by the applicant and the clock was restarted.
- During its meeting on 12-14 October 2011, 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, and the clock was stopped on 24/10/2011 in compliance with Art. 18(3) of Regulation (EC) No 1924/2006.
- On 03/11/2011, EFSA received the requested information as submitted by the applicant and the clock was restarted.
- During its meeting on 24/11/2011, the NDA Panel, having evaluated the data submitted, adopted an opinion on the scientific substantiation of a health claim related to Bimuno® GOS and reducing gastro-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

⁴ European Parliament and Council (2006). 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. Official Journal of the European Union OJ L 404, 30.12.2006. Corrigendum OJ L 12, 18.1.2007, p. 3–18.

opinion on the scientific substantiation of a health claim related to: Bimuno[®] GOS and reducing gastro-intestinal discomfort.

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation to the marketing of Bimuno[®] GOS, a positive assessment of its safety, nor a decision on whether Bimuno[®] GOS 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.

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: Clasado Ltd., 5 Canon Harnett Court, Wolverton Mill, Milton Keynes, MK12 5NF. United Kingdom.

The applicant includes a request for the protection of proprietary data in accordance with Article 21 of Regulation (EC) No 1924/2006 for nine published studies (Depeint et al. (2008); Drakoularakou et al. (2010); Goulas et al. (2007); Searle et al. (2009, 2010); Silk et al. (2009); Tzortzis et al. (2005a, b); Vulevic et al. (2008)) and for analytical and stability data for the manufacturing process. The applicant also indicates proprietary rights for one unpublished study report (Clasado Ltd.'s study report).

Food/constituent as stated by the applicant

According to the applicant, the food constituents are galacto-oligosaccharides from Bimuno[®] (Bimuno[®] GOS) which are a mixture of β -linked galacto-oligosaccharides (β -1 \rightarrow 3, β -1 \rightarrow 4, β -1 \rightarrow 6) with a degree of polymerisation ranging between 2 and 5, and α -linked galacto-oligosaccharides (α -1 \rightarrow 6) with a degree of polymerisation of 2.

Health relationship as claimed by the applicant

According to the applicant, Bimuno[®] GOS acts to reduce bloating, flatulence and intestinal pain. These effects can be described collectively as "intestinal discomfort". The mechanism for these effects is not known, but may involve bifidogenesis that is an effect associated with several markers for gastro-intestinal health, and the preventative and inhibitory effects of Bimuno[®] galacto-oligosaccharides on enteropathogenic organisms in the gastro-intestinal tract. In this way, galacto-oligosaccharides from Bimuno[®] help to maintain the health of the gastro-intestinal tract. According to the applicant, reducing gastro-intestinal discomfort may improve quality of life and is beneficial to human health.

Wording of the health claim as proposed by the applicant

The applicant proposes the following wording for the health claim: "Regular daily consumption of 1.37 g galacto-oligosaccharides from Bimuno[®] may reduce intestinal discomfort".

Specific conditions of use as proposed by the applicant

According to the applicant, 1.37 g of galacto-oligosaccharides from Bimuno[®] to be consumed once per day for a minimum of 7 days.

ASSESSMENT

1. Characterisation of the food/constituent

The food constituent that is the subject of the health claim is Bimuno[®] GOS, a mixture of β -galacto-oligosaccharides which is produced through conversion of lactose by enzymes from *Bifidobacterium bifidum* NCIMB 41171.

Based on chemical analyses that were provided on 5 batches, the Bimuno[®] powder contains a mixture of β -galacto-oligosaccharides (Bimuno[®] GOS, 47-53 %), lactose (25-35 %), glucose (6-10 %) and galactose (4-7 %).

Bimuno[®] GOS comprises a mixture of β -linked galacto-oligosaccharides (β -1 \rightarrow 3, β -1 \rightarrow 4, β -1 \rightarrow 6) and α -linked galacto-oligosaccharides (α -1 \rightarrow 6). The ratio of β -linked galacto-oligosaccharides to α -linked galacto-oligosaccharides is 93:7.

The results from the stability tests showed that the Bimuno[®] powder was stable for up to two years.

The Panel considers that the food constituent, Bimuno[®] GOS, which is the subject of the health claim, is sufficiently characterised.

2. Relevance of the claimed effect to human health

The claimed effect is “reduce bloating, flatulence and intestinal pain, that can be described collectively as intestinal discomfort”. The target population as proposed by the applicant is individuals over 3 years of age.

The Panel considers that reducing gastro-intestinal discomfort is a beneficial physiological effect.

3. Scientific substantiation of the claimed effect

The applicant performed a literature search through PubMed with the following key words: galactooligosaccharide bifidogenic, galactooligosaccharide bloating, galactooligosaccharide digestion, galactooligosaccharide gastrointestinal, galactooligosaccharide prebiotic and prebiotic bifidogenic. A time frame for the search is not reported.

Based on the search criteria, the applicant identified the following studies as being pertinent to the health claim: eight randomised, controlled, human intervention studies (Bouhnik et al. 2004; Depeint et al. 2008; Drakoularakou et al. 2010; Piirainen et al., 2008; Shadid et al., 2007; Silk et al., 2009; Vulevic et al., 2008; Clasado Ltd.’s study report, unpublished); two human observational studies (Bouhnik et al., 1997; Teuri et al., 1998), and three non-human studies (Searle et al., 2009, 2010; Tzortzis et al., 2005a).

Three of the human intervention studies provided addressed the effects of Bimuno[®] GOS on symptoms related to gastro-intestinal discomfort (Drakoularakou et al., 2010; Clasado Ltd., unpublished; Silk et al., 2009). One of these (Drakoularakou et al., 2010) was designed to investigate the effects of Bimuno[®] GOS on the incidence of travellers’ diarrhoea in adults. Upon EFSA’s request, the applicant clarified that this study was not provided to substantiate an effect of Bimuno[®] GOS on gastro-intestinal discomfort, but rather to indicate that Bimuno[®] GOS is “bifidogenic” and does not present untoward effects. The Panel considers that no conclusions can be drawn from this study for the scientific substantiation of the claim.

A placebo-controlled, randomised, double-blind, cross-over study by Clasado Ltd. (unpublished, claimed as proprietary by the applicant) investigated the effects of daily consumption of Bimuno[®] GOS on symptoms related to gastro-intestinal discomfort. A total of 91 volunteers (21-65 years; mean age 35.5 years, 53 females and 38 males) were recruited on the basis of suffering from gastro-intestinal discomfort and having a predicted probability of functional bowel disease of more than 75 % estimated by a bowel disease questionnaire. Subjects were randomised to consume daily 2.75 g of Bimuno[®] (1.37 g of Bimuno[®] GOS; n=45) or 2.75 g maltodextrin (control; n=46) for two weeks each with a two-week washout period in between. The Panel notes that the duration of the intervention is shorter than the minimum duration of 4 weeks which is considered appropriate in the field to assess changes in symptoms related to gastro-intestinal discomfort (Irvine et al., 2006). Study outcomes, compliance (return of empty product sachets), medication use, and adverse events were assessed weekly at clinic visits during the two treatment periods. The primary outcomes of the study were incidence, duration and severity of bloating (defined as feeling bloated or experiencing abdominal fullness often), occurrence of abdominal pain/discomfort, flatulence, need to defecate,

global assessment of relief, and general well being. Secondary outcomes were stool frequency, stool consistency and mood. Bloating, abdominal pain/discomfort, flatulence and need to defecate were recorded daily and weekly using a 4-point Likert scale; general well-being was assessed using the IBS-36 questionnaire; stool frequency and consistency were assessed using a 7-point Bristol stool scale; the effect on mood was assessed using the Hospital Anxiety and Depression scale. A total of 83 volunteers (42 in the intervention and 41 in the control group) completed the study and entered the analysis. The Panel notes that the statistical analysis was conducted on the complete case population only, and that no intention-to-treat (ITT) analysis was provided. From the information provided, the Panel also notes that data were analysed by combining the results obtained during the first and second treatment periods for the Bimuno® GOS and placebo, and that multiplicity of outcomes was not taken into account. EFSA requested the applicant to provide the full study report and a statistical re-analysis of the data which would be appropriate for cross-over designs. The applicant provided a brief summary report including limited information on a statistical analysis which again compared the effects of the Bimuno® GOS and control products after pooling the corresponding treatment periods of the two interventions, and which did not take into account repeated measures. The Panel considers that the statistical analysis provided is inappropriate for the study design. The Panel notes the important methodological limitations of this study (e.g. short duration, inappropriate statistical analysis for cross-over designs, and no ITT analysis) and considers that no conclusions can be drawn from this study for the scientific substantiation of the claim.

The applicant provided a randomised, placebo-controlled intervention study (Silk et al., 2009) in subjects with Rome II positive irritable bowel syndrome (IBS). After a two-week run-in period, 60 subjects were randomised into one of the following study arms: a) placebo (7 g/day maltodextrin); b) Bimuno® 7 g/day; c) Bimuno® 3.5 g/day. All subjects received placebo (maltodextrin) at the doses of 3.5 or 7 g/day for four weeks, followed by a two-week “washout” period, and then either placebo (7 g/d maltodextrin) or Bimuno® at doses of 3.5 or 7 g/day (containing 1.32 or 2.65 g/day Bimuno® GOS, respectively) for four weeks. The primary outcome of the study was changes in the gut bifidobacterial population. Secondary outcomes were bowel movements, stool consistency, bloating, abdominal pain, flatulence, a composite score of symptoms, and anxiety and depression scores, and subjective global assessment of relief. A total of 44 subjects completed the study and entered data analysis. The Panel notes the high dropout rate (25 %), that the statistical analyses were conducted on the complete case population only whereas no ITT analysis was provided, and that multiplicity of outcomes was not taken into account in data analysis. The authors report that all data were analysed by repeated measures ANOVA (RM-ANOVA) “taking into account the cross-over design”. However, the Panel notes that subjects were not randomised according to a cross-over design. The authors also report that the ANOVA model considered volunteer, treatment period [baseline (week 2), end of placebo (week 6) and end of the intervention (week 12)] and treatment as fixed effects, and subject measurements as random effects. However, the Panel notes that results for outcome measures related to gastro-intestinal symptoms were reported in a table for each study arm as baseline and end values for the first (placebo, weeks 2 and 6) and second (intervention, weeks 8 and 12) treatment periods, and that only within-group comparisons between baseline and end of each (placebo and intervention) period (paired t-tests), and between-group comparisons for each time point (unclear how these were performed), were provided. Results of the RM-ANOVA model to assess the effects of treatment were not reported. In order to proceed with the scientific assessment of this study, EFSA requested the applicant to provide the full study report and further information on data analyses. The applicant provided a brief summary report including limited information on a statistical analysis for which it was unclear which data were used (time points included) and whether repeated measures were taken into account. The Panel considers that the additional information provided was insufficient to assess the effects of treatment on the outcome measures of interest. The Panel notes the important methodological limitations of this study (e.g. high dropout rate, multiplicity of outcomes not taken into account in data analysis, statistical methods and results insufficiently described, and no ITT analysis) and considers that no conclusions can be drawn from this study for the scientific substantiation of the claim.

Human studies were provided by the applicant on the effects of Bimuno® GOS (Depeint et al. 2008; Drakoularakou et al. 2010, Vulevic et al. 2008) or other galacto-oligosaccharides from a variety of sources (Bouhnik et al. 2004, 1997; Piirainen et al., 2008; Shadid et al., 2007; Teuri et al., 1998) on the gut microbiota. Animal and *in vitro* studies provided by the applicant also investigated the effect of Bimuno® GOS on the gut microbiota (Searle et al., 2009, 2010; Tzortzis et al., 2005a). The Panel considers that the evidence provided does not establish that an effect of Bimuno® GOS on bifidobacteria *per se* is sufficient to predict an effect of Bimuno® GOS on gastro-intestinal discomfort *in vivo* in humans.

The Panel considers that no human studies have been provided from which conclusions can be drawn for the scientific substantiation of the claim.

The Panel concludes that a cause and effect relationship has not been established between the consumption of Bimuno® GOS and reducing gastro-intestinal discomfort.

CONCLUSIONS

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

- The food constituent, Bimuno® GOS, which is the subject of the health claim, is sufficiently characterised.
- The claimed effect is “reduce bloating, flatulence and intestinal pain, that can be described collectively as intestinal discomfort”. The target population as proposed by the applicant is individuals over 3 years of age. Reducing gastro-intestinal discomfort is a beneficial physiological effect.
- A cause and effect relationship has not been established between the consumption of Bimuno® GOS and reducing gastro-intestinal discomfort.

DOCUMENTATION PROVIDED TO EFSA

Health claim application on Bimuno® GOS and reducing gastro-intestinal discomfort pursuant to Article 13(5) of Regulation (EC) No 1924/2006 (Claim serial No: 0299_UK). June 2011. Submitted by Clasado Ltd.

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GLOSSARY / ABBREVIATIONS

IBS	Irritable Bowel Syndrome
ITT	Intention-to-treat
NCIMB	National Collections of Industrial, Marine and Food Bacteria
RM-ANOVA	Repeated Measures ANOVA