Scientific publications fact sheets

ACTIVIA® GUT SCIENCE HUB

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Information for Healthcare Professionals and Scientists only

Scientific publications fact sheets by Activia®

Note:

The strain *Bifidobacterium animalis* subsp. *lactis.* DN-173 010 is deposited in the Collection Nationale de Cultures de Micro-Organismes (CNCM), at the Institute Pasteur (Paris, France) as *Bifidobacterium animalis* subsp. *lactis* CNCM I-2494.
The nomenclature DN-173 010 can be found in several scientific publications. In this document, the strain is designated as *B. lactis* CNCM I-2494.

Introduction

01. Activia® Efficacy Studies

Studies on healthy population

- Marteau *et al.,* 2019
- Marteau *et al.,* 2013
- Guyonnet *et al.,* 2009b
- Guyonnet *et al.,* 2009a

Studies on IBS-C population

- Agrawal *et al.,* 2009
- Guyonnet *et al.,* 2007

02. Activia® Mechanism of Action Studies: Survival

- Rochet *et al.,* 2008
- Collado *et al.,* 2006
- Duez *et al.,* 2000
- Pochart *et al.,* 1992
- Berrada *et al.,* 1991

03. Activia® Mechanism of Action Studies: Gut Microbiota

- Veiga *et al.,* 2014
- McNulty *et al.,* 2011

04. Activia® Mechanism of Action Studies: Host

- Tillisch *et al.,* 2013
- Yang *et al.,* 2008
- Marteau *et al.,* 2002
- Bouvier *et al.,* 2001

05. Activia® Reviews and Meta-Analysis

- Eales *et al.,* 2016
- Waitzberg *et al.,* 2015

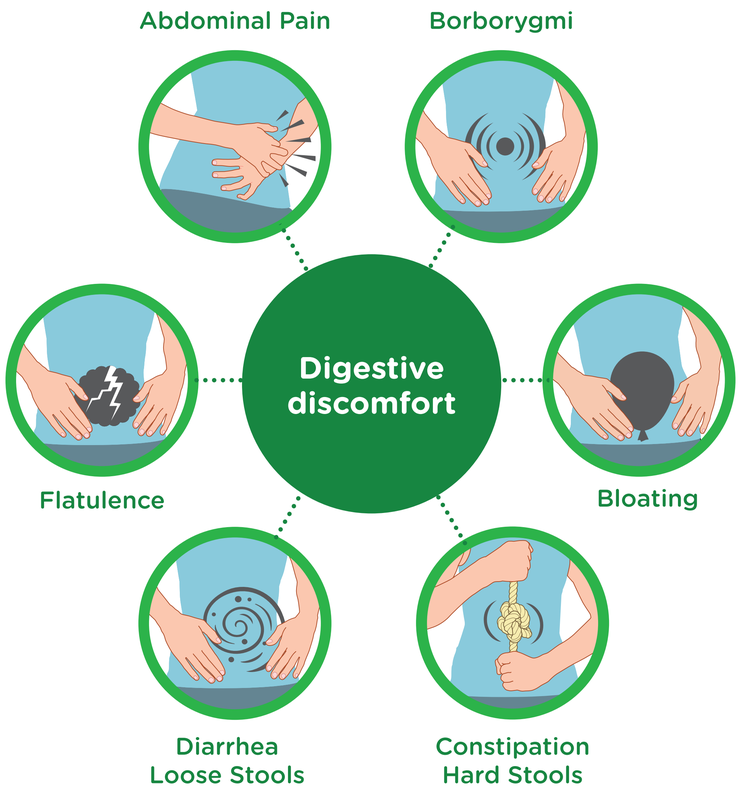
IBS: Irritable Bowel Syndrome

IBS-C: Irritable Bowel Syndrome constipation predominant (IBS-C is a sub-type of Irritable Bowel Syndrome in which the patient's prime symptom picture consists of chronic constipation)

Introduction

About digestive discomfort

Digestive functions play a key role in maintaining or improving health status[1]. The concept of gastrointestinal (GI) comfort is often associated to an absence of GI symptoms or, more generally, a perception of well-being or pleasant sensations1. It can be affected by digestive complaints such as abdominal pain, flatulence, bloating, borborygmi and altered bowel habit (constipation, diarrhea), leading to discomfort (cf. figure below).



Although the type, severity, and frequency of these digestive symptoms vary between subjects, more than half of the general population frequently experience one or more of these digestive complaints[1-4]. It is recognized that these symptoms can impact the quality of life.

Since gastrointestinal comfort depends on the perception of sensations from the gut (e.g. bloating, flatulence) and on bowel function, it is measured with overall assessments that integrate all these parameters[5-7]. These assessments should be performed with validated tools, questionnaires, which allow subjects to self-report their discomfort level[7].

About Research on Activia®

Research on Activia® started in the eighties with the identification and selection of the Bifidus strain contained in Activia®, *Bifidobacterium lactis* CNCM I-2494. Investigation on the Bifidus properties went on in the nineties with first clinical studies showing that this strain survives the passage through the GI tract.

Clinical studies were then conducted to investigate the effect of Activia® consumption on digestive comfort. 3 of these studies were done on healthy subjects, and 2 of them on Irritable Bowel Syndrome (IBS) subjects (IBS population being an appropriate model to investigate the effect of a dietary intervention on GI comfort). These five clinical studies evaluated digestive comfort through a global assessment of gastrointestinal well-being and combination of several digestive symptoms with validated questionnaires.

In parallel, Danone Nutricia Research's scientists evaluated possible mode of action of the product, always with the collaboration of international research facilities and experts.

A recent meta-analysis conducted with international experts in gastroenterology reviewed the science on Activia® and digestive comfort in healthy population using the highest methodology standards.

Timeline of Activia® research's milestones

- **1985** — **Identification and selection of *B. lactis* strain.**
  Understanding/characterization of the Bifidus strain selected.
- **1988** — **1st results on clinical trial, survival.**
- **1991** — **1st international publication on Activia®, survival** (Berrada 1991).
- **2000** — **Bifidus strain deposited by Danone in the Institute Pasteur collection: CNCM I-2494.**
- **2001** — **1st clinical trial on the understanding of the effect of our Bifidus strain - healthy** (Bouvier 2001).
- **2002** — **1st clinical trial on the understanding of the effect of Activia® - healthy** (Marteau 2002).
- **2007** — **1st clinical trial on the effect of Activia® on digestive discomfort – IBS** (Guyonnet 2007).
- **2009** — **1st clinical trial on the effect of Activia® on digestive discomfort - healthy** (Guyonnet 2009b).
  1st clinical trial on the effect of Activia® fruits on digestive discomfort - healthy (Guyonnet 2009a).
  1st clinical trial on the effect of Activia® on digestive discomfort with an objective marker – IBS (Agrawal 2009).
- **2011** — **1st clinical trial on gut microbiota changes with Activia** (McNulty 2011).
- **2013** — **1st clinical trial on gut-brain axis and probiotic food, i.e. Activia® – healthy** (Tillisch 2013).
  Repetition of Guyonnet 2009b study and pooled analysis of both studies – healthy (Marteau 2013).
- **2015** — **1st review on Activia® and digestive discomfort – healthy** (Waitzberg 2013).
- **2016** — **1st meta-analysis on Activia® and digestive discomfort – healthy** (Eales 2016).
- **2019** — ***Post-hoc* pooled analysis on Activia® health effects after 2 weeks of consumption**

References:

1. *Cummings JH, Antoine JM, Azpiroz F, Bourdet-Sicard R, Brandtzaeg P, Calder PC, Gibson GR, Guarner F, Isolauri E, Pannemans D, Shortt C, Tuijtelaars S, Watzl B. PASSCLAIM – gut health and immunity. Eur J Nut 2004* **2.** *Heaton KW, O'Donnell LJ, Braddon FE, Mountford RA, Hughes AO, Cripps PJ. Symptoms of irritable bowel syndrome in a British urban community: consulters and nonconsulters. Gastroenterology 1992.* **3.** *Leibbrand, R., Cuntz, U., & Hiller, W. (2002). Assessment of functional gastrointestinal disorders using the Gastro-Questionnaire. International journal of behavioral medicine 2002.* **4.** *van Kerkhoven LA, Eikendal T, Laheij RJ, van Oijen MG, Jansen JB. Gastrointestinal symptoms are still common in a general Western population. Neth J Med 2008;66(1):18-22.* **5.** *Longstreth, G.F., Thompson, W.G., Chey, W.D., Houghton, L.A., Mearin, F. and Spiller, R.C. 2006. - Functional bowel disorders– Gastroenterology 2006.* **6.** *Corazziari, E., Bytzer, P., Delvaux, M., Holtmann, G., Malagelada, J.R., Morris, J.,Muller-Lissner, S., Spiller, R.C., Tack, J. and Whorwell, P.J. - Clinical trial guidelines for pharmacological treatment of irritable bowel syndrome - Aliment. Pharmacol. Ther. 2003.* **7.** *Irvine, E.J., Witehead, W.E., Chey, W.D., Matsueda, K., Shaw, M., Talley, N.J. and Veldhuyzen van Zanten, S.J.O. - Design of treatment trials for functional gastrointestinal disorders - Gastroenterology 2006*

01.

Activia® Efficacy Studies

Studies on healthy population

- Marteau *et al.*, 2019
- Marteau *et al.*, 2013
- Guyonnet *et al.*, 2009b
- Guyonnet *et al.*, 2009a

Studies on IBS-C population

- Agrawal *et al.*, 2009
- Guyonnet *et al.*, 2007

Studies on Healthy Population

01 | Activia® Efficacy Studies

Marteau *et al.,* 2019

Marteau P., Le Nevé B., Quinquis L., Pichon C., Whorwell P.
A post-hoc pooled analysis of two previously published clinical studies (randomized, double-blind, controlled) with a fermented milk containing probiotic Bifidobacterium lactis CNCM I-2494 in healthy women reporting minor digestive symptoms after 4 weeks of consumption.
Nutrients. 2019 Jan; 11(1): 92. (Open access)

This publication presents results from a pooled analysis of two previous studies (Marteau et al., 2013, Guyonnet et al., 2009b) that demonstrated a significant effect of Activia in reducing minor digestive issues after 4 weeks consumption (2x125g per day).

Pooled analysis

Analysis methodology

A pooled analysis was performed from two previously published studies (Stop 1 study: Guyonnet et al., 2009b, Stop 2 study: Marteau et al., 2013) on women with minor digestive symptoms consuming Activia or a control product during 4 weeks.
A total of 538 participants provided weekly assessments of bloating, abdominal pain/discomfort, flatulence, borborygmi/rumbling stomach from which a composite score ranging from 0 to 16 was calculated. At baseline in one study (Stop2; n = 336), dietary fibre consumption was recorded (using phone interview by dietetician) and physical activity classified as high, moderate or low (using the questionnaire IPAQ). The speed of Activia's effect was assessed by a repeated measure analysis of variance measuring the change from baseline for the composite score of digestive symptoms.

Objectives

- To determine the speed of improvement (i.e minimal duration of consumption required to implement an improvement) of abdominal discomfort with Activia

- To establish whether lifestyle components such as fibre intake or physical exercise may influence this effect.

Results

Digestive symptoms

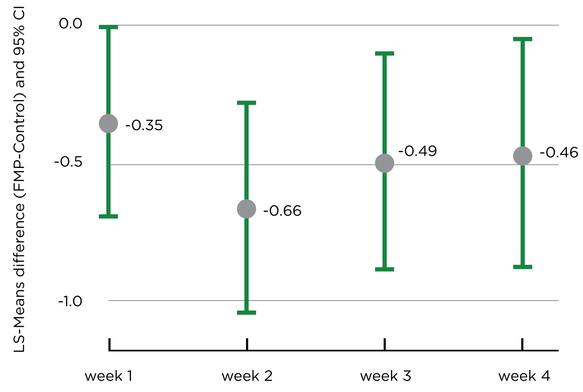
Activia consumption resulted in a significant decrease in the composite score of digestive symptoms (bloating, abdominal pain/discomfort, flatulence, borborygmi/rumbling) after only 2 weeks with the pooled data at:

- Week 1 (-0.35 [-0.69, 0.00]; p = 0.05),
- Week 2 -0.66 [-1.04, -0.27]; p < 0.001),
- Week 3 (-0.49 [-0.89, -0.10]; p = 0.01)
- and Week 4 (-0.46 [-0.88, -0.04]; p = 0.03).

Diet

We observed in Marteau et al., 2013 study that the interactions fibre intake-by-product group, physical activity-by-product group and time-by-product group were not statistically significant.

Linear mix model estimates by visit on change from baseline in composite score of digestive symptoms



Conclusion of the clinical study and the pooled analysis

This post-hoc analysis shows an effect of Activia in reducing minor digestive issues after only 2 weeks consumption of 2x125g per day.

This effect is independent of the amount of dietary fibre consumed and the level of physical activity before starting Activia consumption (i.e. baseline), meaning that fibre intake and physical activity are not confounding factors in these studies.

Studies on Healthy Population

01 | Activia® Efficacy Studies

Marteau *et al.*, 2013

Marteau P, Guyonnet D, Lafaye de Micheaux P, Gelu S. A randomized, double-blind, controlled study and pooled analysis of two identical trials of fermented milk containing probiotic Bifidobacterium lactis CNCM I-2494 in healthy women reporting minor digestive symptoms. Neurogastroenterol Motil. 2013 Apr;25(4):331-e252.

The publication presents the results of both a new clinical study that is a repetition of the Guyonnet 2009b* study and the pooled analysis of this new study together with the first study.

clinical study

Study Methodology

The study was a randomized, double-blind, controlled, parallel clinical trial on 324 women (18-60 yo) with minor digestive symptoms but without diagnosed gastrointestinal (GI) disorders. The subjects consumed daily either 2x125g servings of either Activia® (n=162) or a non-fermented dairy product with low content of lactose (lactose content similar to the test product) (n=162), over 4 weeks.

Measured Outcomes

Gastrointestinal well-being *(main outcome)*

- Overall gastrointestestinal well-being assessment.
- 3-point Likert scale (worse, no change, better).
- Rate of responders (subjects reporting an improvement (i.e. "better") during at least 2 weeks over the 4 weeks of product consumption).
- Weekly self-evaluation during the 4-week period of product consumption.

Digestive symptoms

- Score of frequency of 4 individual symptoms (abdominal pain/discomfort, bloating, flatulence/ passage of gas, borborygmi/rumbling stomach).
- 5-point Likert scale (from none to every day) for individual symptoms.
- Weekly self-evaluation during baseline and product consumption period.

Diet

- 3 non-consecutive 24-hour dietary recalls undertaken by dieticians, combined with a food and nutrient composition database.
- At baseline and during the last week of product consumption.
- Composite score of the 4 digestive symptoms.

Results

Gastrointestinal well-being

After 4 weeks of product consumption, a non-significant improvement in GI well-being was observed in the Activia® group compared to the control group (OR=1.20 [95% CI 0.87;1.66]). Similarly, the percentage of responders was higher in the Activia® group compared to the control group without significant difference (54.3% vs. 46.3% respectively, OR=1.38 [95% CI 0.89;2.14]).

Digestive symptoms

Over the 4 weeks of product consumption, results showed a significant decrease in the composite score of digestive symptoms in the Activia® group compared to the control group (LSmean=-0.42 [95% CI -0.81;-0.03], p=0.033). No significant difference was observed for single symptoms.

Diet

No significant changes in nutrient intake between groups were observed during the 4-week intervention period.

** Guyonnet D, Schlumberger A, Mhamdi L, Jakob S, Chassany O. Fermented milk containing Bifidobacterium lactis DN-173 010 improves gastrointestinal well-being and digestive symptoms in women reporting minor digestive symptoms: a randomised, doubleblind, parallel, controlled study. British Journal of Nutrition. 2009 Dec; 102(11):1654-1662.*

pooled analysis

Study Methodology

As the clinical study was a repetition (same protocol) of the study of Guyonnet 2009b, the data from these

2 studies were combined in a pooled analysis. This pooled analysis included all randomized subjects of the 2 studies (n=538, intention to treat population). The objective of this pooled analysis was to assess the efficacy of Activia® on both overall assessment of GI well-being and composite score of digestive symptoms with an increased sample size and thus a greater statistical power.

Measured Outcomes

Gastrointestinal well-being *(main outcome)*

(Same as clinical Study)

Digestive symptoms

(Same as clinical Study)

Results

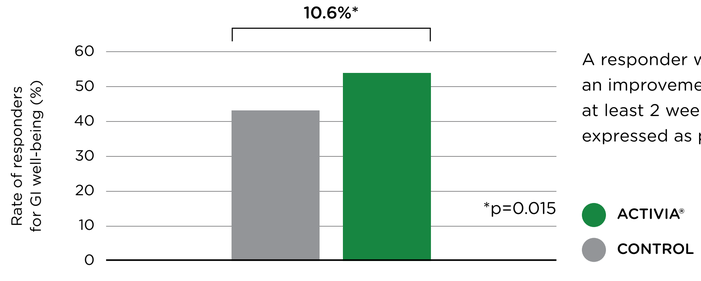
Gastrointestinal well-being

The percentage of women reporting an improvement in their GI well-being was significantly higher in the Activia® group compared to the control group (OR=1.36 [95% CI 1.07;1.73], p=0.014), as well as the percentage of responders for GI well-being (53.2% vs. 42.6% respectively, OR=1.53 [95% CI 1.09;2.16], p=0.015).

Digestive symptoms

A significant decrease of the composite score over the 4-week period was shown in the Activia® group compared to the control group (LSmean=-0.48 [95% CI -0.80;-0.16], p=0.003).

Overall assessment of gastrointestinal well-being (rate of responders) after Activia® or control consumption



A responder was defined as a subject reporting an improvement of its gastrointestinal well-being at least 2 weeks over the 4 weeks; results are expressed as percentage.

Conclusion of the clinical study and the pooled analysis

The replication study confirmed improvements in digestive symptoms but not in GI well-being, in women with minor digestive symptoms consuming daily 2x125g of Activia® during 4 weeks. The pooled analysis of the two trials showed improvements in both GI well-being and digestive symptoms.

These new data support the ability of Activia® to improve GI well-being and reduce digestive symptoms in a population of women reporting mild GI discomfort.

Studies on Healthy Population

01 | Activia® Efficacy Studies

Guyonnet *et al.*, 2009b

*Guyonnet D, Schlumberger A, Mhamdi L, Jakob S, Chassany O. Fermented milk containing Bifidobacterium lactis DN-173 010 improves gastrointestinal well-being and digestive symptoms in women reporting minor digestive symptoms: a randomized, double-blind, parallel, controlled study. British Journal of Nutrition, 2009; 102(11):1654-62.**

Study Methodology

The study was a randomized, double-blind, controlled, parallel clinical trial on 197 women (18–60 yo) with minor digestive symptoms but without gastrointestinal (GI) disorders. The subjects consumed daily 2x125g servings of either Activia® (n=100) or a non-fermented dairy product with low content of lactose (lactose content similar to the test product) (n=97), over 4 weeks. There was an additional follow-up 4 weeks after the cessation of product consumption (washout period).

Measured Outcomes

Gastrointestinal Well-Being *(main outcome)*

- 3-point Likert scale (worse, no change, better) and additional 15-point Likert scale to precise the level of worsening or improvement.
- Weekly self-evaluation during product consumption and washout periods.
- Rate of responders (subjects reporting an improvement (i.e. "better") during at least 2 weeks over the 4 weeks of product consumption).

Digestive Symptoms

- Score of frequency of 4 individual digestive symptoms: abdominal pain/discomfort, bloating, flatulence/passage of gas, borborygmi and rumbling stomach.
- 5-point Likert scale for individual symptoms.
- Weekly self-evaluation during product consumption and washout periods.
- Composite score of the 4 digestive symptoms.

Bowel Function

- Frequency expressed as number of bowel movement/week.
- Consistency evaluated with Bristol Stool Scale.
- Daily self-evaluation during product consumption and washout periods.

Health Related Quality of Life

- FBA (Food Benefit Assessment) and PGWBI (Psychological General Well-Being Index) questionnaires.
- Self-evaluation at baseline, at end of product consumption and at end of washout period.

Results

DOUBLE-BLIND PERIOD:

Gastrointestinal Well-Being

- The percentage of women reporting an improvement in their GI well-being was significantly higher in the Activia® group vs. control group (OR=1.69, [95% CI 1.17;2.45]; p=0.006), as well as the percentage of responders for GI well-being (52.0% vs. 36.1% respectively, OR=1.92 [95% CI 1.09;3.40], p=0.025).

Digestive Symptoms

- Over the 4 weeks of product consumption, results showed a significant decrease in the composite score of digestive symptoms (LS mean=-0.57 [95% CI -1.12;-0.02], p=0.044) and in borborygmi frequency (LS mean=-0.22 [95% CI -0.40;-0.04], p=0.016) in the Activia® group compared to the control group.
- The decrease in flatulence frequency was significantly higher in the Activia® group vs. control group at weeks 1, 2 and 4 ($p<0.05$).
- No significant differences were observed in individual scores for bloating, abdominal pain or discomfort.

Bowel Function

A significant (p=0.02) improvement of the stool consistency was observed in the Activia® group vs. the control group. Stool frequency did not differ between groups.

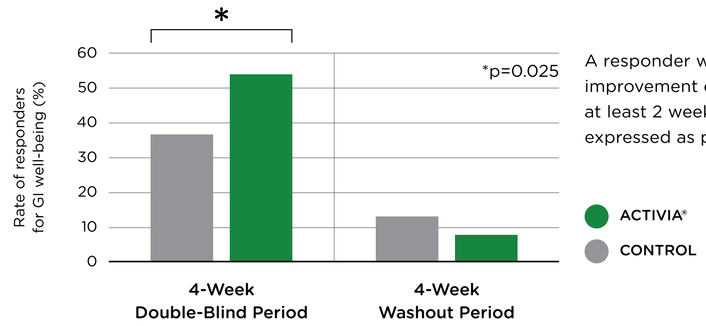
Health Related Quality of Life

- FBA digestive comfort dimension score significantly increased (p=0.027) after 4 weeks of product consumption in the Activia® group vs. control group (FBA questionnaire). No difference was observed between groups for other HRQoL dimensions. PGWBI scores did not differ between groups over time.

WASHOUT PERIOD:

- The percentage of women reporting an improvement in their GI well-being did not differ significantly between groups at the end of the washout period.
- The percentage of responders strongly decreased without significant differences between the Activia® and the control groups (8.0% vs.11.3%; OR 0.68 [95%CI 0.26;1.77]).
- The composite score of digestive symptoms significantly decreased ($p<0.05$) over the 4 weeks in the control group when compared with the Activia® group. No significant difference in the changes of frequency for each individual symptom was observed between the groups.
- No differences were observed between groups for stool frequency, consistency or HRQoL dimensions.

Overall assessment of GI well-being (rate of responders)



A responder was defined as a subject reporting an improvement of their gastrointestinal well-being at least 2 weeks over the 4 weeks; results are expressed as percentage.

Conclusion

Daily consumption of 2x125g servings of Activia® during 4 weeks may improve GI well-being and digestive symptoms in the general population of women reporting minor digestive symptoms. The effect of Activia® was no longer observed once consumption was stopped.

** DN 173-010 is a Danone strain code for B. lactis CNCM I-2494*

Studies on Healthy Population

01 | Activia® Efficacy Studies

Guyonnet *et al.*, 2009a

*Guyonnet D, Woodcock A, Stefani B, Trevisan C, Hall C. Fermented milk containing Bifidobacterium lactis DN-173 010 improved self-reported digestive comfort amongst a general population of adults. A randomized, open-label, controlled, pilot study. Journal of Digestive Diseases, 2009; 10: 61-70.**

Study Methodology

The study was a randomized, controlled, open-label, parallel group trial on 360 healthy volunteers (18–65 yo), with self-reported digestive discomfort and a normal stool frequency. They consumed daily either 1x125g serving (n=144) or 2x125g servings (n=147) of Activia®, or followed their usual diet without intervention (n=69) over 14 days.

Measured Outcomes

Digestive Comfort *(main outcome)*

- General change in digestive comfort.
- 5-point Likert scale.
- Self-evaluation after 14 days of product consumption.

Digestive Symptoms

- 20-item questionnaire.
- 5-point Likert scale.
- Self-evaluation at baseline and at the end of product consumption.

Results

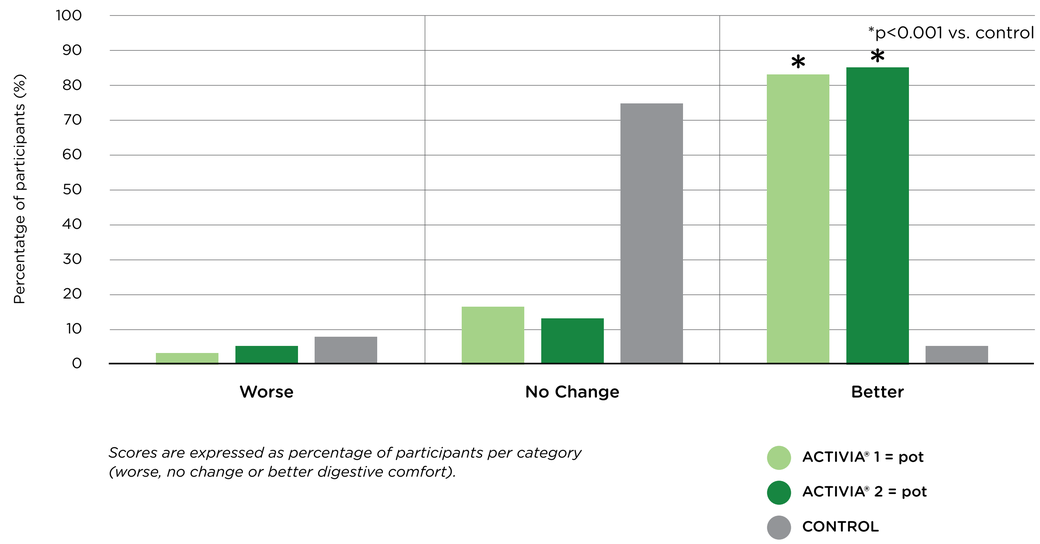
Change in General Digestive Comfort

- The percentage of subjects reporting an improvement of digestive comfort was significantly higher in both Activia® groups (1-pot group 82.5%; 2-pot group 84.3%; p<0.001) vs. the control group (2.9%).
- There was no significant difference between 1-pot and 2-pot groups.

Digestive Symptoms

For both Activia® groups, there was a significant greater improvement (p<0.001) vs. control for almost all symptoms, including bloated feeling and excessive or trapped wind.

Change in perceived digestive comfort after Activia® or control consumption



Scores are expressed as percentage of participants per category (worse, no change or better digestive comfort).

Conclusion

Daily consumption of 1 or 2x125g of Activia® servings during 14 days may exert positive effects on self-reported digestive comfort in a general population of healthy adults in real-life conditions. Beyond this global improvement, the bother from several digestive symptoms may be reduced in a high and significant percentage of participants.

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Studies on IBS-C Population

01 | Activia® Efficacy Studies

Agrawal *et al.*, 2009

*Agrawal A, Houghton L.A, Morris J, Reilly B, Guyonnet D, Goupil-Feuillerat N, Schlumberger A, Jakob S, Whorwell P.J. Clinical trial: the effects of a fermented milk product containing Bifidobacterium lactis DN-173 010 on abdominal distension and gastrointestinal transit in irritable bowel syndrome with constipation. Alimentary Pharmacology and Therapeutics, 2009; 29(1): 104-114.**

Study Methodology

The study was a randomized, controlled, double-blind, parallel group study on 38 women (18-70 yo) with Irritable Bowel Syndrome with predominant constipation (IBS-C). The subjects consumed daily 2x125g servings of either Activia® (n=18) or a non-fermented dairy product with low content of lactose (lactose content similar to the test product) (n=20), over 4 weeks.

Measured Outcomes

Abdominal Distension *(main outcome)*

- Abdominal girth measured with plethysmography method.
- Continuous measurement during 24 hours at baseline and after 4 weeks of product consumption.

Colonic and Small Bowel Transit Times

- Radiopaque marker (colonic transit time) and hydrogen breath test methods (small bowel transit time).
- Evaluation at baseline and after 4 weeks of product consumption.

IBS and Digestive Symptoms

- Score of severity of individual symptoms (abdominal pain/discomfort, bloating, flatulence) and overall IBS symptom severity.
- 6-point Likert scale (from none to very severe).
- Daily self-evaluation during baseline and product consumption periods.

Bowel Function

- Frequency expressed as number of bowel movement/week.
- Consistency evaluated with Bristol Stool Scale.
- Daily self-evaluation during product consumption period.

Results

Abdominal Distension

After 4 weeks of product consumption, a trend towards a reduction in mean abdominal distension during the day (area under the curve (AUC) values, -1.52 cm [95% CI 3.33;0.39], p=0.096) and a significant reduction in the percentage change in maximal distension (Activia®: -77.1% vs. control: -28.6%, p<0.05) were observed in the Activia® group, in comparison with the control group.

Colonic and Small Bowel Transit Times

Colonic and small bowel transit times were significantly reduced in the Activia® group, in comparison with the control group (-12.2h, [95%CI -22.8;-1.6], p=0.026 and -1.2h, [95%CI -2.3;0.0], p=0.049, respectively).

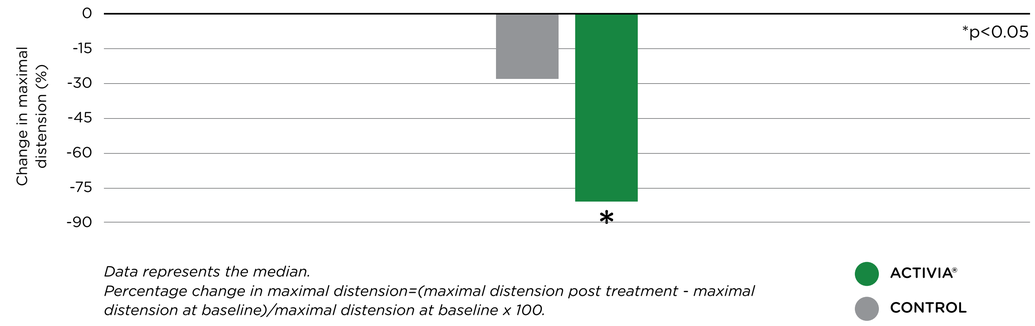
IBS and Digestive Symptoms

- Over the 4 weeks of Activia® consumption, overall symptom severity significantly improved (-0.5, [95% CI -1.0;-0.05], p=0.032).
- Abdominal pain/discomfort significantly decreased (-0.5, [95% CI -1.0;0], p=0.044), and bloating (-0.6, 95% CI [-1.1, 0], p=0.059) and flatulence (-0.4, [95% CI -1.0;0.1], p=0.092) tended to reduce, compared with control group.

Bowel Function

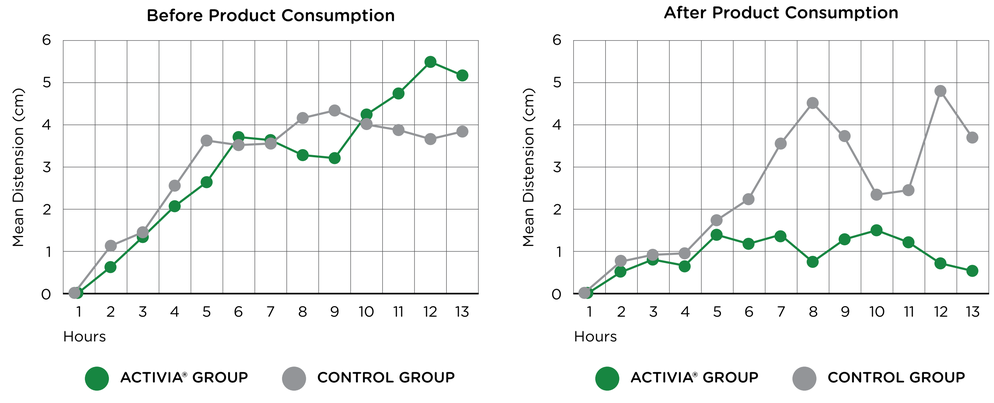
A trend to a normalization of stool consistency (-0.4, [95% CI -0.82;0.01], p=0.058) was also observed without modification of bowel movement frequency.

Percentage change in maximal distension after Activia® or control consumption



Data represents the median.
Percentage change in maximal distension=(maximal distension post treatment - maximal distension at baseline)/maximal distension at baseline x 100.

Mean abdominal distension before and after Activia® or control consumption



Conclusion

Daily consumption of 2x125g servings of Activia® over 4 weeks may reduce abdominal distension in association with acceleration of colonic and small bowel transit times in women with IBS-C. Activia® may also improve digestive comfort by reducing overall IBS symptom severity and digestive symptoms.

** DN 173-010 is a Danone strain code for B. lactis CNCM I-2494*

Studies on IBS-C Population

01 | Activia® Efficacy Studies

Guyonnet *et al.*, 2007

*Guyonnet D, Chassany O, Ducrotte P, Picard C, Mouret M, Mercier C.H, Matuchansky C. Effect of a fermented milk containing Bifidobacterium animalis DN-173 010 on the health-related quality of life and symptoms in irritable bowel syndrome in adults in primary care: a multicentre, randomized, double-blind, controlled trial. Alimentary Pharmacology and Therapeutics, 2007; 26 (3): 475-486.**

Study Methodology

In this randomized, controlled, double-blind, parallel study, 267 subjects (18-65 yo) with Irritable Bowel Syndrome with predominant constipation (IBS-C) consumed daily 2x125g servings of either Activia® (n=135) or a heat-treated yoghurt containing non-living bacteria (n=132), over 6 weeks.

Measured Outcomes

Health-Related Quality of Life *(main outcome)*

- Digestive discomfort dimension of the Functional Digestive Disorder Quality of Life questionnaire (FDDQL).
- Self-evaluation at baseline and after 3 and 6 weeks of product consumption.
- Rate of responders (subjects having an improvement ≥10% of digestive discomfort score vs. baseline).

Global Digestive Symptoms

- 7-point Likert scale.
- Self-evaluation after 3 and 6 weeks of product consumption.

Bloating and Abdominal Pain

- 6-points Likert scale.
- Self-evaluation at baseline and at weeks 3 and 6 of product consumption.

Bowel Function

- Stool frequency expressed as number of bowel movement/week.
- Stool consistency evaluated with Bristol Stool Scale.
- Daily self-evaluation.

Results

Health-Related Quality Of Life

- The FDDQL digestive discomfort score improved ($p<0.001$) in both groups at week 3 (Activia®: 10.7 +/- 14.5; control: 7.5 +/- 16.5) and week 6 (Activia®: 12.2 +/- 16.2; control: 13.5 +/- 19.3).
- The responder rate for the discomfort dimension of the FDDQL questionnaire was significantly higher at week 3 in the Activia® group (65.2%) vs. the control group (47.7%) ($p=0.003$). No significant difference was observed at week 6.

Global Digestive Symptoms

- The evolution of global digestive symptoms scores did not differ between groups at weeks 3 and 6.

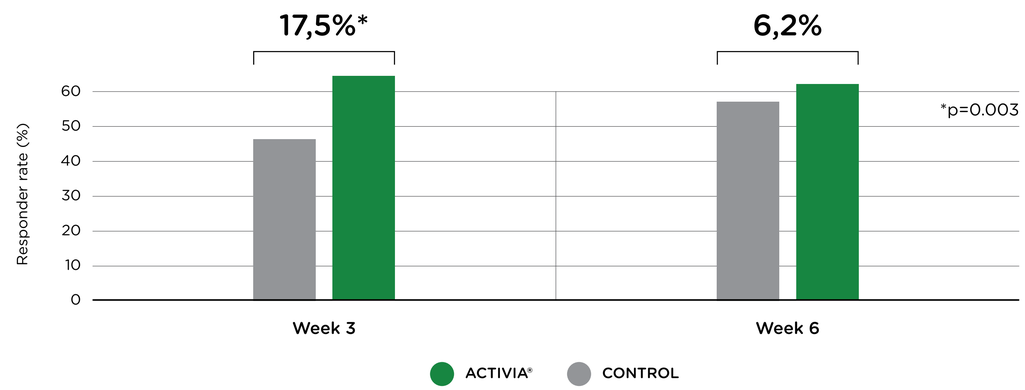
Bloating and Abdominal Pain

- Bloating score significantly improved in both groups as compared to baseline ($p<0.001$), this improvement being significantly higher in Activia® group vs. control at week 3 ($p=0.03$).
- Abdominal pain significantly ($p<0.001$) improved in both groups as compared to baseline without difference between groups.

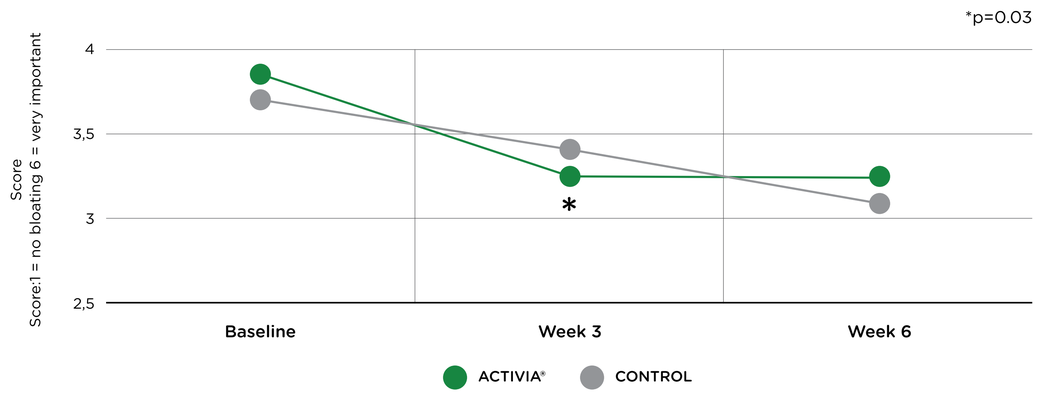
Bowel Function

- In a subgroup of subjects with less than 3 stools / week (n=19), stool frequency significantly increased over 6 weeks in the Activia® group vs. the control group ($p<0.001$).

Rate of responders for digestive comfort dimension after 3 and 6 weeks of Activia® or control consumption



Bloating before and after 3 and 6 weeks of Activia® or control consumption



Conclusion

Daily consumption of 2x125g servings of Activia® during 6 weeks may have a beneficial effect of Activia® on the FDDQL digestive discomfort score and bloating in subjects with IBS-C. A positive effect on stool frequency in subjects having less than 3 stools per week was also observed.

*** DN 173-010 is a Danone strain code for B. lactis CNCM I-2494*

02.

Activia® Mechanism of Action Studies:

Survival

- Rochet *et al.*, 2008
- Collado *et al.*, 2006
- Duez *et al.*, 2000
- Pochart *et al.*, 1992
- Borrada *et al.*, 1991

02 | Activia® Mechanism of Action Studies: Survival

Rochet
et al., 2008

*Rochet V, Rigottier-Gois L, Ledaire A, Andrieux C, Sutren M, Rabot S, Mogenet A, Bresson J.L., Cools S, Picard C, Goupil-Feuillerat N, Doré J. Survival of Bifidobacterium animalis DN-173 010 in the fecal gut microbiota after administration in lyophilised form or in fermented product - A randomized study in healthy adults. Journal of Molecular Microbiology and Biotechnology, 2008; 14: 128-136.**

Study Methodology

In this randomized, open, parallel study, 12 healthy subjects (24-46 yo) consumed daily either 3x125g servings ($6.6x10^{10}$ CFU/day) of Activia® (n=6) or 1g ($2.1x10^{11}$ CFU/day) of freeze-dried powder of *B. lactis* CNCM I-2494 (n=6), over 7 days. The follow-up period lasted 10 days.

Measured Outcomes

Detection of Bifidobacteria in Human Fecal Samples

- Quantification of *Bifidobacterium* genus (Beeren's agar pH 5, not including *B. lactis* CNCM I-2494 strain).
- Quantification of *B. animalis* species (Beeren's agar pH 5.5 and colony immunoblotting method).
- Evaluation at baseline, and each week of product consumption and follow-up periods.

Recovery of *B. lactis* CNCM I-2494

- Molecular and biochemical approaches (Fluorescent *In Situ* Hybridization (FISH) and Polymerase Chain Reaction (PCR)-Temporal Temperature Gradient Gel Electrophoresis (PCR-TTGE)).
- Evaluation at baseline, and each week of product consumption and follow-up periods.

Determination of Fecal Enzyme Activities and Metabolites

- Biochemical analysis.

Results

- According to the quantification by the colony immunoblotting method, the mean number of *B. lactis* CNCM I-2494 was ≥ 10^8 CFU/g of feces, in 5 out of 6 subjects, in both groups, after 7 days of product consumption.
- With PCR-TTGE, *B. lactis* CNCM I-2494 patterns were detected for 11 out of 12 subjects. No major modifications were observed in either the dominant members of the fecal gut microbiota or their activities.

Conclusion

After the daily consumption of 3x125g servings of Activia® or 1g of freeze-dried powder during 10 days, *B. lactis* CNCM I-2494 survived passage through the gastrointestinal tract.

** DN 173-010 is a Danone strain code for B. lactis CNCM I-2494*

02 | Activia® Mechanism of Action Studies: Survival

Collado *et al.*, 2006

*Collado M.C, Moreno Y, Cobo J.M, Mateos J.A, Hernández M. Molecular detection of Bifidobacterium animalis DN-173 010 in human feces during fermented milk administration. Food Research International, 2006; 39: 530-535.**

Study Methodology

In this non-randomized, non-controlled, open trial including 12 healthy volunteers (25-40 yo), 10 subjects consumed daily 250ml of Activia® (n=10) over 4 weeks. 1 subject ingested no product (negative control) and 1 subject ingested daily 250ml of Activia® for 3 months prior study (positive control). The follow-up period lasted 4 weeks.

Measured Outcomes

Quantitative Detection of Bifidobacteria

- Enumeration by plate counting.
- Fluorescent *In Situ* Hybridization (FISH).
- Evaluation at baseline, and each week of product consumption and follow-up periods.

Identification of *Bifidobacterium* and *B. lactis*

- FISH.
- Polymerase Chain Reaction (PCR) genus- and species-specific.
- Evaluation at baseline, and each week of product consumption and follow-up periods.

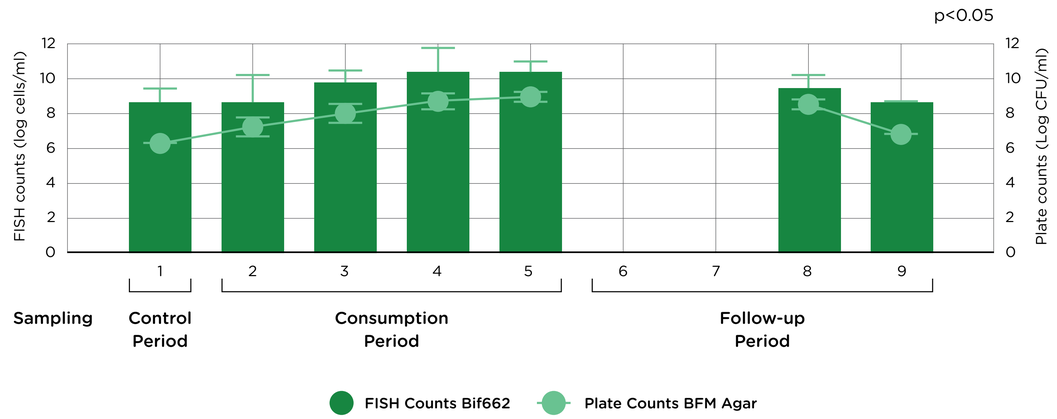
Identification of *B. lactis* CNCM I-2494 Profile

- Amplified Ribosomal DNA Restriction – PCR (ARDRA - PCR).
- Evaluation at baseline, and each week of product consumption and follow-up periods.

Results

- A significant increase of bifidobacteria in feces was observed during product consumption vs. baseline ($p<0.05$).
- 30% of bifidobacteria were identified as *B. lactis* by PCR after 2 weeks of product consumption (90% after 4 weeks). 40% of bifidobacteria were identified as CNCM I-2494 strain by ARDRA-PCR after 2 weeks of product consumption (60% after 3 weeks and 90% after 4 weeks).
- The number of bifidobacteria genus in the positive and negative controls remained stable over the studied period. No *B. lactis* was detected in the negative control.
- Bifidobacteria count decreased to baseline level 4 weeks after discontinuation of the product. *B. lactis* and *B. lactis* CNCM I-2494 were no more detectable after 4 weeks of follow-up period.

Total bifidobacteria genus counts after consumption of Activia®



Conclusion

After daily consumption of 250ml of Activia® over 4 weeks, *B. lactis* CNCM I-2494 survived passage through the gastrointestinal tract.

** DN 173-010 is a Danone strain code for B. lactis CNCM I-2494*

02 | Activia® Mechanism of Action Studies: Survival

Duez
et al., 2000

Duez H, Pelletier C, Cools S, Aissi E, Cayuela C, Gavini F, Bouquelet S, Neut C, Mengaud J. A colony immunoblotting method for quantitative detection of a Bifidobacterium animalis probiotic strain in human faeces. Journal of Applied Microbiology, 2000; 88:1019-27.

Study Methodology

In this non-randomized, non-controlled, open study, 5 healthy women (20-48 yo) consumed daily 3x125g servings of Activia® over 7 days. A method was developed specifically using a combination of semi-selective cultivation and colony immunoblotting techniques (use of an antiserum produced with *B. lactis* CNCM I-2494 to detect *B. animalis* strains amongst several strains representative of different bifidobacterial species).

Measured Outcomes

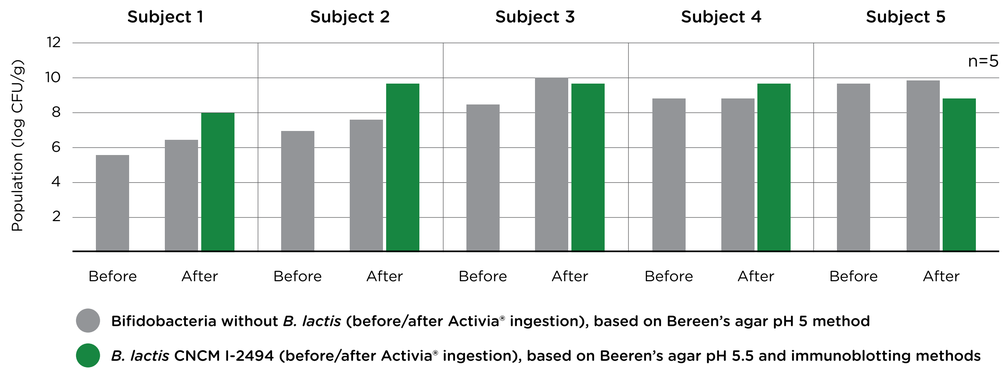
Detection of Bifidobacteria in Human Fecal Samples

- Quantification of bifidobacteria (Beeren's agar pH 5, not including *B. lactis* CNCM I-2494 strain).
- Quantification of *B. animalis* species (Beeren's agar pH 5.5 and colony immunoblotting method).
- Evaluation at baseline and after 7 days of consumption of Activia®.

Results

No colonies of *B. animalis* were detected in any of the fecal samples before ingestion of Activia®. After 7 days of Activia® consumption, the fecal population of *B. lactis* CNCM I-2494 was about 10^8 CFU/g (in 1 subject) and 10^9 CFU/g (in the 4 others).

Enumeration of bifidobacteria and *B. lactis* cncm i-2494 population in fecal samples of five human volunteers before and after one week ingestion of Activia®



Conclusion

After daily consumption of 3x125g servings of Activia® during one week, *B. lactis* CNCM I-2494 was found to be viable in feces, and thus able to survive the intestinal transit in large quantities.

02 | Activia® Mechanism of Action Studies: Survival

Pochart *et al.*, 1992

Pochart P, Marteau P, Bouhnik Y, Goderel I, Bourlioux P, Rambaud J.C. Survival of Bifidobacteria ingested via fermented milk during their passage through the human small intestine: an in vivo study using intestinal perfusion. American Journal of Clinical Nutrition, 1992; 55:78-80.

Study Methodology

In this randomized, controlled, open study, 6 healthy volunteers (18-30 yo) consumed either 400g of fermented milk containing *B. lactis* CNCM I-2494 or a monitored diet containing no bifidobacteria species.

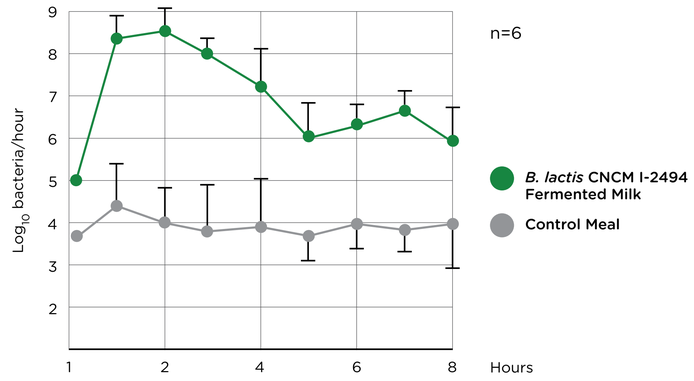
Measured Outcomes

Quantification of viable bifidobacteria reaching the terminal ileum (enumeration by plate counting in ileal perfusion, throughout the 8 hours following product ingestion).

Results

- In the control group, the ileal flow rate of viable bifidobacteria remained stable and low throughout the experiment (around $1x10^4$ CFU/h).
- In the Activia® group, a significant increase in the flow of bifidobacteria was observed in all subjects reaching a peak of $6.3x10^8$ CFU/hour after around 2 hours and remained at a higher level (above $1x10^6$ CFU/h) compared to the control group for the rest of experiment.
- The mean number of bifidobacteria recovered from the terminal ileum was around 10^9 CFU.

Flow rate of bifidobacteria through the ileum after ingestion of *B. lactis* cncm i-2494 fermented milk or control meal



Conclusion

After consumption of 400g of fermented milk containing *B. lactis* CNCM I-2494, ileal flow of bifidobacteria increased significantly. After 8 hours, a large quantity of the strain was recovered in the terminal ileum, indicating that ingested bifidobacteria reached the colon.

** DN 173-010 is a Danone strain code for B. lactis CNCM I-2494*

02 | Activia® Mechanism of Action Studies: Survival

Berrada *et al.*, 1991

Berrada N, Lemeland J.F, Laroche G, Thouvenot P, Piaia M. Bifidobacterium from fermented milks: Survival during gastric transit. Journal of Dairy Science, 1991; 74:409-413.

Study Methodology

The study was a randomized, double-blind, cross-over trial. Both *in vivo* survival (A) and gastric emptying rate (B) were studied.
A: 10 healthy volunteers (20-45 yo) received 250g of Activia® and a compared product (another commercially available fermented milk containing *Bifidobacterium*) in two separate sessions in randomized order.
B: 12 healthy volunteers (22-25 yo) received 250g of Activia® and a compared product (another commercially available fermented milk containing *Bifidobacterium*) in two separate sessions in randomized order.

Measured Outcomes

- **A group:** Survival of *Bifidobacterium* strains (Samples collected using a gastric tube immediately and 30, 60 and 90 minutes after ingestion; enumeration by plate counting).
- **B group:** Gastric emptying rate (detection of 99m-Tc-technetium-labelled solution of rhenium sulfur colloids incorporated in ingested fermented milk, by Scintigraphy, every 10 minutes, over 3 hours).

Results

- After 90 minutes of gastric transit, *Bifidobacterium* population from Activia® decreased by less than 2 log units. *Bifidobacterium* population in the compared product decreased by 4 log units. The difference between the survival of *Bifidobacterium* strains was significant ($p<0.001$).
- There was no significant difference in gastric emptying between Activia® and the compared product.

Conclusion

After consumption of 250g of Activia®, *B. lactis* CNCM I-2494 survived gastric transit.

03.

Activia® Mechanism of Action Studies:

Gut Microbiota

Veiga *et al.*, 2014

McNulty *et al.*, 2011

03 | Activia® Mechanism of Action Studies: Gut Microbiota

Veiga *et al.*, 1992

Veiga P., Pons N., Agrawal A., Oozeer R., Guyonnet D., Brazeilles R., Faurie J.M., van Hylckama Vlieg J.E., Houghton L.A., Whorwell P.J., Ehrlich S.D., Kennedy S.P. Changes of the human gut microbiome induced by a fermented milk product. Scientific Reports. 2014 Sep 11;4:6328

Study Methodology

In this randomized, controlled, double-blind, parallel-group clinical trial*, 28 subjects with Irritable Bowel Syndrome with predominant constipation (IBS-C, Rome III criteria) received 2x125g of either Activia® (n=13) or a non-fermented dairy product with low content of lactose (lactose content similar to the test product) (n=15) daily during 4 weeks. Stools samples were collected before and after the consumption period.
In addition, an *in vitro* human colonic fermentation model was inoculated with the samples of 2 healthy donors and kept stable for 5 weeks. This model was used to investigate the effects of Activia® on production of bacterial metabolites, namely short chain fatty acids (SCFA).

Measured Outcomes

Fecal Abundance of Bacterial Species Contained in Activia®

- Sequencing.
- Evaluation before and after Activia® consumption.

Identification of Bacteria Species Modulated by the Consumption of Activia®

- Sequencing, metagenomics and bioinformatics technologies: whole genome sequencing, mapping on human gut microbiome genes catalog, gene-centric clustering approach.
- Evaluation before and after product consumption period.

Identification of metabolic pathways of modulated species

- Metabolic reconstruction.
- Evaluation after product consumption period.

Evaluation of SCFA Production

- *In vitro* colonic fermentation model.
- Evaluation before and after product consumption period.

Results

Identification of Bacteria Species Modulated by the Consumption of Activia®

Consumption of Activia® during 4 weeks stimulated 5 resident gut species: *B. dentium* and 4 unknown species identified thanks to the gene-centric clustering approach and called hereafter MetaGenomic Species (MGS). Three species, including the pathobiont *Bilophila wadsworthia,* were inhibited.

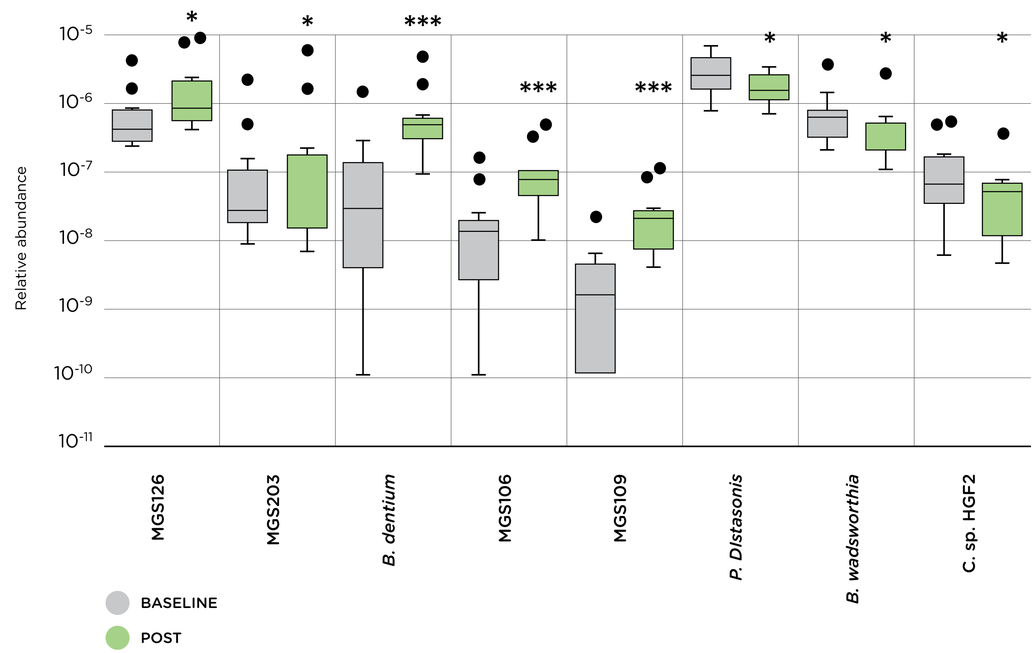
Identification of Metabolic Pathways of Modulated Species

Metabolic modeling indicated that genes involved in butyrate production were detected in 2 MGS stimulated by Activia®.

Evaluation of SCFA Production

In *in vitro* colonic model, the addition of Activia® led to a significant increase of butyrate and total SCFA production compared to baseline.

Abundance of modulated species in Activia® group (baseline and after consumption)



Conclusion

Daily consumption of 2x125g of Activia® led to the modulation of some bacterial species, but no global shift in the gut microbiota was observed. It was also found that consumption of Activia® may stimulate butyrate production.

This clinical trial corresponds to the study published in Agrawal 2009
** DN 173-010 is a Danone strain code for B. lactis CNCM I-2494*

03 | Activia® Mechanism of Action Studies: Gut Microbiota

McNulty *et al.*, 2011

McNulty N.P, Yatsunenko T, Hsiao A, Faith J.J, Muegge B.D, Goodman A.L, Henrissat B, Oozeer R, Cools-Portier S, Gobert G, Chervaux C, Knights D, Lozupone C.A, Knight R, Duncan A.E, Bain J.R, Muehlbauer M.J, Newgard C.B, Heath A.C, Gordon J.I. The impact of a consortium of fermented milk strains on the gut microbiome of gnotobiotic mice and monozygotic twins. Science Translation Medicine, 2011; 3(106):106ra106.

Study Methodology

Two approaches: a controlled human study and a "humanized" animal model.

Human study: 7 healthy female adult monozygotic twin pairs consumed daily 2x113g servings of Activia® during 7 weeks.

Animal model: 10 germ-free mice, colonized with 15 well-characterized bacteria originating from human gut, received either 1x2 gavages within 24h or 3x2 gavages within 24h (over 3 weeks) of the 5 bacterial strains contained in Activia® (2.10^7 CFU in total for each gavage).

Measured Outcomes

HUMAN STUDY: Quantification of *Bifidobacterium lactis* in Feces

- qPCR.
- Evaluation before, during and after the consumption period.

Identification of Dominant Gut Microbiota Composition

- Sequencing technologies on bacteria from feces (Metagenomics = which bacteria are there?).
- Evaluation before, during and after the consumption period.

Gene Expression of Gut Microbiota

- Sequencing technologies (Metatranscriptomics = what are bacteria doing?).
- Evaluation before, during and after the consumption period.

ANIMAL MODEL: Identification of Dominant Gut Microbiota Composition

- Sequencing technologies on bacteria from feces (Metagenomics).
- Evaluation pre-treatment, during treatment, post-treatment.

Gene Expression of Gut Microbiota

- Sequencing technologies (Metatranscriptomics).
- Evaluation pre-treatment, during treatment, post-treatment.

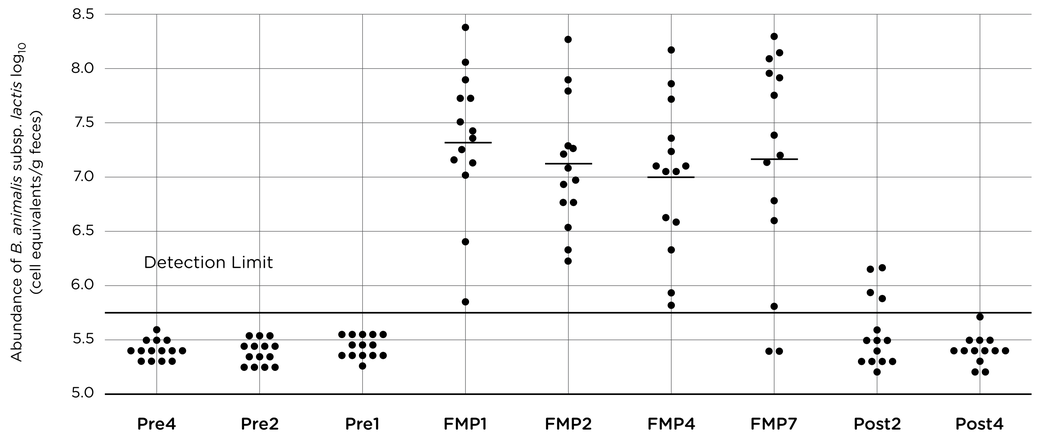
Identification of Metabolic Pathways

- Measurement of metabolites in urine samples (Metabolomics).
- 3 measures before colonization, the day of the first inoculation, post-treatment.

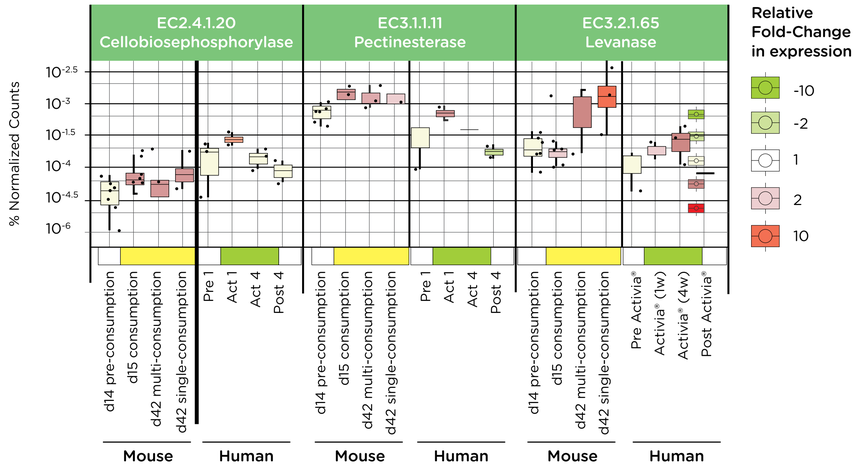
Results

- Among the 14 healthy humans, from the week 1 to the week 7 of Activia® consumption, the level of *B. lactis* CNCM I-2494 was high in feces. 4 weeks after the cessation of Activia® consumption, levels decreased to below the limits of detection in all participants.
- No detection of significant impact of Activia® consumption on global dominant gut microbiota composition in humans, and minor modification in mice (no statistical significance).
- Gene expression of the gut microbiota was modulated:
  - Activia® (product and strains) could promote the efficacy of utilization of plant-derived polysaccharides by the gut microbiota.
  - Activia® (product and strains) could promote the production of short chain fatty acids by the gut microbiota.
- *B. lactis* CNCM I-2494 is active in the gut and appears to utilize xylo-oligosaccharides (XOS) that mainly originate from plant dietary components.

Levels of *Bifidobacterium animalis subsp. lactis* in human fecal samples collected prior to, during and after consumption of Activia®



Mouse and human gut microbial communities share transcriptional responses to Activia® involving ecs (enzyme commission) related to carbohydrate metabolism



Conclusion

After the daily consumption of 2x113g servings of Activia® during 7 days, *B. lactis* CNCM I-2494 survived passage through the gastrointestinal tract. When healthy people consumed Activia®, the global composition of the gut microbiota (bacteria living in the colon) remained stable, but the gene expression of some gut microbes was modulated.

04.

Activia® Mechanism of Action Studies:

Host

- Tillisch *et al.*, 2013
- Yang *et al.*, 2008
- Marteau *et al.*, 2002
- Bouvier *et al.*, 2001

04 | Activia® Mechanism of Action Studies: Host

Tillisch *et al.*, 2013

Tillisch K, Labus J, Kilpatrick L, Jiang Z, Stains J, Ebrat B, Guyonnet D, Legrain-Raspaud S, Trotin B, Naliboff B, Mayer EA. Consumption of Fermented Milk Product with Probiotic Modulates Brain Activity. Gastroenterology, 2013 Jun; 144(7):1394-1401

This study on the modulation of the gut-brain axis gave new leads into the understanding of the mode of action of Activia® on the reduction of digestive discomfort and its symptoms. It was the first study in humans assessing the action of chronic intake of a fermented milk product with probiotic on brain activity.

Study Methodology

In this double-blind, randomized, controlled study, 38 healthy women (18-50 yo) were divided in 3 groups

- The first group (n=14; Fermented Milk Probiotic Product (FMPP) group) consumed daily 2x125g servings of Activia® during 4 weeks.
- The second group (n=11; Control) consumed daily 2x125g servings of a non-fermented milk product with low content of lactose (lactose content similar to the test product) during 4 weeks.
- The third group (n=13; No intervention (No In) group) did not consume any product.

Measured Outcomes

Activity of a Network of Brain Regions and Activity of Specific Regions of the Brain

- Functional magnetic resonance imaging (fMRI).
- During standardized emotional faces attention task (viewing negative affect (fear and danger) faces or viewing geometric forms for control)
- At resting state (eyes closed, no challenge). Analyses of scanners were based on changes in Blood Oxygenation Level Dependent (BOLD) contrasts. Brain activity was compared between pre-intervention and post-intervention, but also between groups (FMPP vs. CONTROL, FMPP vs. NO IN and CONTROL vs. NO IN).
- Evaluation before and at the end of the 4-week intervention period.

Results

Activity Of A Network Of Brain Regions

- Reactivity of a network of brain regions after a negative emotional attention task was significantly reduced ($p<0.0001$) in the FMPP group, compared to Control and No In groups.
- Changes in brain activity induced by consumption of Activia® at resting state are positively correlated to the emotional faces attention task results ($p<0.0001$).
- 4 weeks of Activia® consumption were significantly associated with modifications in a resting state network (periaqueductal gray (PAG) seeded) ($p<0.0001$) compared to CONTROL and No In groups.

Activity of Specific Regions of the Brain

- Analyses of 2 specific brain regions within the network of interest (interoceptive and somatosensory regions) were also performed. Consumption of Activia® is associated with modulation of reactivity of these 2 specific regions to an emotional attention task, compared to No In ($p<0.004$, $p<0.005$, respectively) and Control groups ($p<0.03$, $p<0.02$, respectively).
- The evaluation of the effect of a 4-week period of Activia® consumption on affection and mood via questionnaires (HAD, PSS, PANAS) did not show any change from baseline in the subjects participating in the study.

Conclusion

Daily consumption of 2x125g servings of Activia® over 4 weeks may modulate activity of specific brain regions in healthy women.

04 | Activia® Mechanism of Action Studies: Host

Yang
et al., 2008

*Yang Y, He M, Hu G, Wei J, Pages P, Yang X, Bourdu-Naturel S. Effect of a fermented milk containing Bifidobacterium lactis DN-173 010 on Chinese constipated women. World Journal of Gastroenterology, 2008; 14(40): 6237-6243.**

Study Methodology

This study was a randomized, double-blind, placebo-controlled, parallel group study. 135 healthy Chinese women with constipation (less than 3 stools/week; increased stool hardness; non-organic constipation and habitual constipation) (25-65 yo), consumed daily 100g of either Activia® (n=67) or an acidified milk containing non-living bacteria (n=68), over 2 weeks.

Measured Outcomes

Bowel Function *(main outcome)*

- Frequency expressed as number of bowel movement/week.
- Consistency evaluated with Bristol Stool Scale.
- Evaluation at baseline, after 1 and 2 weeks of product consumption.

Defecation condition

- 4-grade score.
- Self-evaluation at baseline, after 1 and 2 weeks of product consumption.

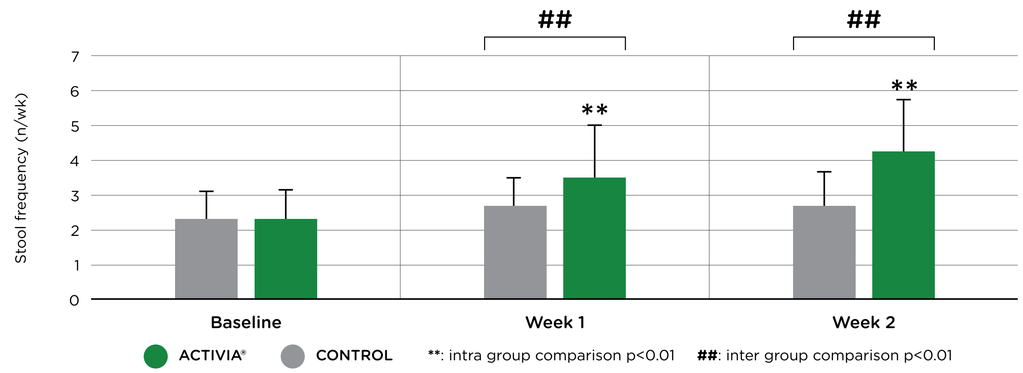
Diet

- 3 non-consecutive 48-hour dietary recalls.
- At baseline, after 1 week and after 2 weeks of product consumption.

Results

After 1 and 2 weeks of Activia® consumption, stool frequency significantly increased ($p<0.01$) and defecation conditions ($p<0.01$) and stool consistency significantly improved (week 1: $p<0.01$, week 2: $p<0.05$), in comparison to the control group.

Stool frequency after one or two weeks of Activia® or control consumption



Conclusion

Daily consumption of 100g of Activia® during 2 weeks may improve stool frequency and consistency as well as defecation conditions, in Chinese women with constipation.

** DN 173-010 is a Danone strain code for B. lactis CNCM I-2494*

04 | Activia® Mechanism of Action Studies: Host

Marteau *et al.*, 2002

*Marteau P, Cuillerier E, Méance S, Gerhardt MF, Myara A, Bouvier M, Bouley C, Tondu F, Bommelaer G, Grimaud JC. Bifidobacterium animalis strain DN-173 010 shortens the colonic transit time in healthy women: a double-blind, randomized, controlled study. Alimentary Pharmacol & Therap, 2002;16:587-93.**

Study Methodology

In this randomized, controlled, double-blind, multicenter, cross-over study, 32 healthy women (18-45 yo) were divided in two groups. The first group (n=17) started with 3x125g servings of Activia® daily, then consumed 3x125g servings of a yoghurt daily. The second group (n=15) began with the yoghurt and then consumed Activia® (same quantities daily). Each consumption period lasted 10 days, with a 10 days interval period between ingestion of each product.

Measured Outcomes

Colonic Transit Times

- Total *(main outcome),* right, left and sigmoid transit times.
- Radio-opaque marker method.
- Evaluation at baseline and after each product consumption period.

Fecal Bile Salts, Ph, Microbial Mass and Weight

- Evaluation at baseline and after each product consumption period.

Results

- In the total population, both colonic and sigmoid transit times were significantly ($p<0.05$) shortened in the Activia® group, compared to the control group, but no difference was observed vs. baseline.
- In the subgroup of subjects with an initial transit time >40 hours, both colonic and sigmoid transit times were significantly ($p<0.05$) shortened in the Activia® group vs. the control group and vs. baseline.
- Fecal mass, pH, bacterial mass and bile acids were not significantly modified.

Colonic and sigmoid transit times in whole population and women with colonic transit time >40h

	Whole population (n=32)			Subjects with colonic transit time >40h (n=21)		
Transit Time (h)	Baseline	Activia®	Control	Baseline	Activia®	Control
Colonic	55.2 ± 28.0^{ab}	51.5 ± 30.2^{a}	60.7 ± 27.1^{b}	70.4 ± 21.8^{a}	62.4 ± 29.8^{b}	71.9 ± 26.5^{a}
Sigmoid	25.2 ± 18.9^{ab}	21.6 ± 14.9^{a}	26.8 ± 14.2^{b}	32.8 ± 18.3^{a}	27.1 ± 14.9^{b}	32.1 ± 13.1^{a}

Values: mean ± SD
Two values having different letters within a single line are statistically significantly different ($p<0.05$).

Conclusion

Daily consumption of 3x125g servings of Activia® may reduce colonic transit time in women. This effect was more pronounced in women with initial slower transit time.

** DN 173-010 is a Danone strain code for B. lactis CNCM I-2494*

04 | Activia® Mechanism of Action Studies: Host

Bouvier *et al.*, 2001

*Bouvier M., Méance S., Bouley C., Berta J.L., Grimaud J.C. Effect of consumption of a milk fermented by the probiotic strain Bifidobacterium animalis DN-173 010 on colonic transit time in healthy humans. Bioscience Microflora. 2001; 20(2):43-48**

Study Methodology

The study was a double-blind, placebo controlled study with 72 healthy subjects (21-24 yo). Subjects consumed daily either 3x125g of a milk fermented by *B. lactis* CNCM I-2494 (Bifidus group) or a heat-treated milk fermented by *B. lactis* CNCM I-2494 (no viable *B. lactis* CNCM I-2494 strains, control group) during 11 days.

Measured Outcomes

Colonic Transit Times

- Total *(main outcome),* right, left and sigmoid transit times.
- Radio-opaque marker method.
- Evaluation at baseline and after product consumption period.

Results

- The reduction of the total colonic transit time after consumption period was significantly greater in the Bifidus group than in the control group (p<0,05, -6,8 hr and +0,5hr respectively).
- For right, left and sigmoid transit times, only the reduction of sigmoid transit time in the Bifidus group after consumption period vs. baseline was significant.

Total colonic transit time before and after ingestion of bifidus or control milk

	Bifidus (n=36)			Control (n=36)		
Transit Time (h)	Before	After	Delta	Before	After	Delta
Total colonic transit time (hr)	33.0 ± 16.1	26.2 ± 14.7*	-6.8* (-20.6%)	30.1 ± 16.4	30.6 ± 17.4	+0.5 (+1.6%)
Sigmoid transit time (hr)	9.5 ± 8.6	5.8 ± 7.7•	-3.7 (-38.9%)	7.9 ± 6.3	7.1 ± 8.7	-0.8 (-10.1%)

*** Significantly different from initial (Wilcox on test; p<0.05)**

• Bifidus group significantly different from Control group (Mann-Whitney test; p<0.05)

Conclusion

Daily consumption of 3x125g of a milk fermented by *B. lactis* CNCM I-2494 may lead to a significant reduction of the total colonic transit time compared to a control group.

** DN 173-010 is a Danone strain code for B. lactis CNCM I-2494*

05.

Activia® Reviews and Meta-Analysis

Eales *et al.*, 2016

Waitzberg *et al.*, 2015

05 | Activia® Reviews and Meta-Analysis

Eales *et al.*, 2016

Eales J., Gibson P.R., Whorwell P.J., Kellow J., Yellowlees A., Perry R., Edwards M., King S., Wood H., Glanville J. Systematic review and meta-analysis: the effects of fermented milk with Bifidobacterium lactis CNCM I-2494 and lactic acid bacteria on gastrointestinal discomfort in the general adult population. Therap Adv Gastroenterol. 2016. First published on October 9, 2016.

Study Methodology

This systematic review with meta-analysis aims to evaluate the effectiveness of Activia® on gastrointestinal (GI) discomfort in healthy population. It was carried out according to the Cochrane Handbook for Systematic Reviews.

Study Selection

- Healthy population with minimal GI discomfort.
- Consumption of Activia® compared to control product for at least four weeks.
- Eligible outcomes: the effectiveness of Activia® on GI discomfort or comfort/well-being measured by a global assessment, and/or a composite score of digestive symptoms (sum of the score of frequency of individual symptoms).
- Double-blind randomized controlled trials.

Study Quality and Statistical Analysis

- Evaluation of the quality of the studies using Cochrane risk of bias tool.
- Meta-analysis using individual subject data to calculate Odds Ratio (OR) or Standards Mean Difference (SMD) with 95% confidence intervals (CI).

Results

Selected Studies

In total, three trials were included in the review (Marteau 2013, Guyonnet 2009b, Donazzolo 2007 unpublished), with a total number of 598 subjects. All three included studies were considered to have a low risk of bias (i.e. high quality).

Gastrointestinal Discomfort/Well-Being

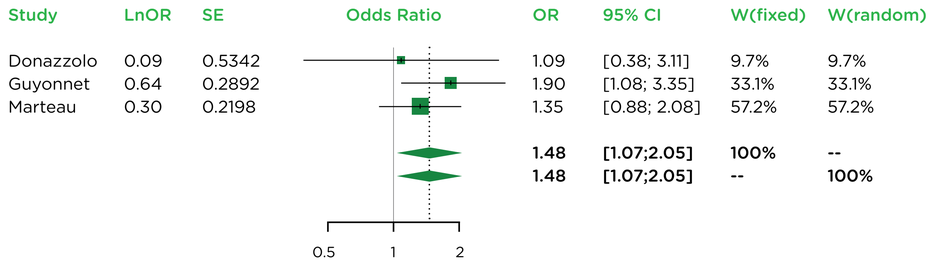
For overall GI discomfort/well-being, results show a significant effect in favor of Activia® (OR = 1.48, [95% CI 1.07;2.05]) after 4 weeks of product consumption. The corresponding number needed to treat was 10.24 [95% CI 5.64; 55.93].

Digestive Symptoms

For composite score of digestive symptoms, results show a significant effect in favor of Activia® (SMD = -0.21, [95% CI -0.37;-0.05]) after 4 weeks of product consumption.

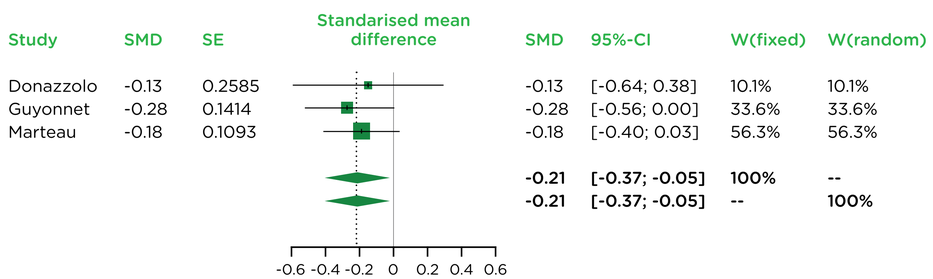
Sensitivity analyses produced similar results for both outcomes, and the heterogeneity of the studies was minimal.

Meta-analysis of studies assessing the effect of Activia® on overall gi discomfort/well-being in the general population



Fixed effect model
Random effects model
Heterogeneity: I-squared=0%, tau-squared=0, p=0.5353

Meta-analysis of studies assessing the effect of Activia® on composite score of digestive symptoms in the general population



Fixed effect model
Random effects model
Heterogeneity: I-squared=0%, tau-squared=0, p=0.8238

Conclusion

This meta-analysis shows that the daily consumption of 2x125g of Activia® is associated with a consistent and significant improvement of outcomes related to GI discomfort in healthy adults. This effect is qualified as modest.

05 | Activia® Reviews and Meta-Analysis

Waitzberg *et al.*, 2016

Waitzberg D.L., Quilici F.A., Michzputen S., Friche Passos M.D.
The effect of probiotic fermented milk that includes Bifidobacterium lactis CNCM I-2494 on the reduction of gastrointestinal discomfort and symptoms in adults: a narrative review.
Nutricion Hospitalaria. 2015 Aug 1;32(n02):501-509

Study Methodology

This narrative review aims to evaluate the effectiveness of Activia® on gastrointestinal (GI) discomfort in healthy adults. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed.

Study Selection

- Randomized controlled trials.
- Consumption of Activia® compared to control product.
- Healthy adults.
- Investigated outcomes related to GI discomfort or comfort.

Study Quality

- Evaluation of the risk of bias using criteria specific to randomized trials.
- Evaluation of the methodological quality of the studies using the Oxford Quality Scale.
- Evaluation of the concealment with the Cochrane Concealment Assessment.

Results

Selected Studies

Two clinical trials (Guyonnet 2009 and Marteau 2013) were included. These studies provided data for 538 healthy subjects and showed low risk of bias and adequate concealment.

The outcomes of the studies were the overall assessment of GI well-being, the percentage of responders for GI well-being (subjects reporting an improvement during at least 2 weeks over the 4 weeks of product consumption) and the composite score of frequency of four GI symptoms.

Gastrointestinal Well-Being

- In the first study (Guyonnet 2009) a significant improvement of GI well-being in the Activia® group vs. the control group was observed (OR = 1.69; [95% CI 1.17, 2.4]). No significant differences were observed in the second study (Marteau 2013 OR = 1.38; [95% CI 0.89, 2.14]). The pooled analysis from the two studies (conducted for Marteau 2013) showed a significant greater improvement in GI well-being in the Activia® group vs. the control group (OR = 1.36; [95%CI 1.07, 1.73]).
- The percentage of responders was significantly higher in the Activia® group vs. the control group in the first study (OR = 1.53; [95% CI 1.09, 2.16]) and not in the second study. A significant positive effect was observed in the pooled analysis (OR = 1.53; [95% CI 1.09, 2.16]).

Gastrointestinal Symptoms

The composite score was significantly decreased in the Activia® group vs. the control group in both studies and in the pooled analysis (p=0.003).

Conclusion

This review found evidence that daily consumption of 2x125g of Activia® may improve GI well-being and digestive symptoms in healthy population with minor GI discomfort.

Information for Healthcare Professionals and Scientists only