

## References

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HELP  
IBS  
SUFFERERS  
GET BACK ON THE  
HIGHWAY TO  
GOOD HEALTH

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# HELP IBS SUFFERERS GET BACK ON THE HIGHWAY TO GOOD HEALTH

**PROBI•MAGE®**  
Sound gut.Sound life.

# OUR INVISIBLE RESIDENTS

They are in air, in water and in earth. They are within us and on us. They are in every crevice, every skin-fold and every orifice leading into our body. Together, their total weight in our body may be close to the average weight of the adult human brain i.e. about 3 lbs or almost 1.4 kgs. In terms of a population count, their number may run into trillions. They are our resident microbes.

We cannot see them or feel them, yet the impact of microbes on our body is profound. Varieties of microbes populate every human and are differently composed in each one. Our birth process, whether natural or caesarean, our food preference, whether vegetarian or otherwise, our residential environment, whether rural or urban and several other factors determine the nature and composition of our microbes.

Contrary to common beliefs which are rooted in concepts of hygiene, microbes are necessary and vitally important residents of the gastrointestinal (GI) system. They maintain and protect the mucosal lining of the gastrointestinal tract. They protect the gut and indeed the entire body, from external infecting-inducing pathogens and most important, help the body digest nutrients for assimilation.

At some time in their lives, most people would have experienced GI disturbances. Depending on symptoms, these can be clinically described by various names - irritable bowel syndrome, bloating, constipation, diarrhea, heartburn, acid reflux, flatulence, intestinal cramps and so on. Our relationship with the microbes within us is necessarily a balanced one. The good microbes block the bad ones and thus



# IBS, UPSETS PATIENTS DOWN TO THE GUT

## A Description of IBS

Irritable Bowel Syndrome is also known as spastic colon, mucous colitis, spastic colitis, nervous stomach, or irritable colon. The descriptions are archaic but all of these reflect the state of patient's gut. IBS is a functional disorder of the gastrointestinal tract.

It is characterized by abdominal pain, which may be temporarily relieved by defecation or expulsion of gas, and also by altered bowel movements due to diarrhoea and/or constipation which may be accompanied by cramps or bloating.

### Irritable Bowel Syndrome

Chronic or recurrent GI symptoms

- Lower abdominal pain/discomfort
- Altered bowel habits
- Bloating

Not explained by structural or biochemical abnormalities

No specific organic pathology has been identified to diagnose IBS. The diagnosis is largely based on meeting symptom criteria defined by Manning, and Rome 1, 2 and 3.

## IBS and HRQoL

IBS is not a life-threatening condition, but its symptoms diminish the sufferer's health-related quality of life<sup>1</sup>. IBS can have an adverse impact on the patient's sense of well-being, increase health-related expenditure and decrease productivity.<sup>1</sup>

### IBS Symptoms Reduce Patient Well Being



### Medical Costs Associated With IBS<sup>37,38</sup>

- Estimated \$8 billion annually in direct costs
- Increased physician visits for both GI and non-GI complaints
- IBS patients incur 74% more health care costs than do non-IBS sufferers

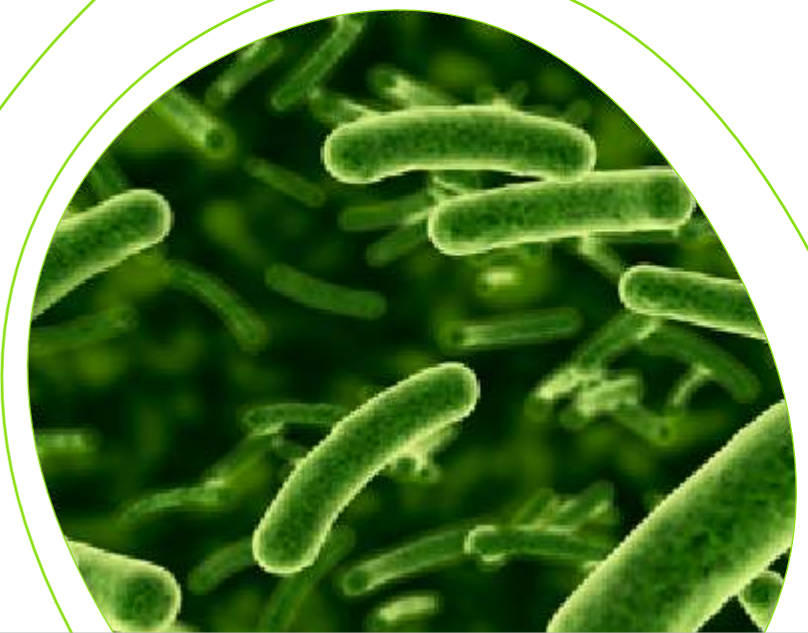
### Impact of IBS on Work<sup>39</sup>

Missed work	:30% (1.7 days)
Reduced days	:46% (3 days)
Turned down promotion	:16%
Changed job, health reasons	:9%
Changed work schedule	:8%

### The sufferer may also report one or more of the following:

- A sensation of incomplete defecation
- Burning pain on defecation
- Urgency to defecate
- Rectal Tenesmus
- Mucorrhea with changes in stool frequency and/or consistency

Other possible gastrointestinal symptoms include heartburn, chest pain, early satiety and flatulence.



# THE IMPORTANCE OF BALANCE IN GUT MICROFLORA

The role of gut microflora in IBS emerges from clinical evidence, from the relationship between gut microflora and GI sensori-motor functions and also from the ability of probiotics to alter these functions, thus improving some symptoms of IBS.

The gut microflora can be compared to a diverse ecosystem existing in a rainforest. These "good" microorganisms play a role in digestion of food, regulation of hormones, production of toxins to repulse pathogens and production of vitamins to keep the gut healthy and the body fit.

A balance in this ecosystem is necessary for good health. If the "bad" microorganisms outnumber the "good" ones, like say, *Lactobacillus*, this can adversely affect health.

## What is a Probiotic?

FAO & WHO have proposed a definition of probiotics which states that probiotics are "live microorganisms which when administered in adequate amounts have a beneficial effect on health of the host."

## Other criteria for a microorganism to be labeled as a probiotic

Besides the criterion of having a beneficial effect on health of the host, the following also have been proposed:<sup>2,3</sup>

Probiotics should be of human origin and be safe for intake as a food and for clinical use. In other words, they should be non-pathogenic, safe on intestinal mucosa and not carry transferable antibiotic resistance genes. They should be susceptible to antibiotics and survive passage through the intestine without being affected by acid or bile. They should be able to adhere to mucosal surface, colonize the intestine and produce antimicrobial substances that antagonize pathogenic bacteria. Finally they should be clinically documented with validated health effects and be stable during processing and storage.

## Probiotic protection of the gut and the body

Probiotics promote endogenous host defense mechanisms and have the following effects:

1. enhance non-immunologic gut defense, by stabilization of the gut microflora.<sup>4</sup>
2. enhance humoral immune responses and thus strengthen the intestine's immunologic barrier.<sup>5,6</sup>
3. stimulate non-specific host resistance to microbial pathogens.<sup>7,8</sup>
4. modulate host immune responses to potentially harmful antigens, with a potential to down-regulate hypersensitivity reactions.<sup>9,10</sup>

## Mechanism of Action of Probiotics

It has been hypothesized that probiotics act by improving the balance of microflora populating the intestine. This is especially relevant in cases of antibiotic induced diarrhea where both beneficial and harmful bacteria are killed by the drug. Probiotics also offer protection to the intestinal wall by competitively inhibiting intestinal attachment by pathogenic bacteria. These pathogens which are suspended in the lumen of the intestine are then washed away. Finally, probiotics strengthen intestinal barrier function and immune function.

The growing understanding of the benefits of probiotics resulted in researchers in Sweden identifying *Lactobacillus plantarum* 299v as a very promising species for the treatment of IBS.





## Lactobacillus plantarum- a natural constituent of fermented foods

Lactobacillus plantarum is commonly found in many fermented food products available worldwide, including sauerkraut, fermented sausages brined olives, Korean kimchi, Nigerian ogi, Ethiopian kocho and sourdough, cassava, grape juice, wine, some cheeses and in dadih, a traditional fermented buffalo milk from Indonesia.<sup>11</sup>

The widespread presence of this organism in foods identified it as an ideal species for further research.

## Important features of Lactobacillus plantarum 299v (LP299V®)

**Clinical studies using Lactobacillus plantarum 299v have shown that this species satisfies the important criteria that can label it as a probiotic, as the following will show:**

### Anti-microbial activity<sup>12</sup>

Lactobacillus plantarum 299v possesses and demonstrates anti-microbial activity (in vitro) against potentially pathogenic bacteria. Its inhibitory effect of against Enterobacteriaceae and Gram-negative anaerobes has been demonstrated in rat models simulating severe clinical conditions.<sup>12</sup>

## Adhesion to intestinal epithelial cells<sup>13</sup>

Lactobacillus plantarum 299v inhibits entero-pathogenic and entero-hemorrhagic Escherichia coli (EPEC/EHEC) adhesion to intestinal epithelial cells in vitro, by inducing mucin expression that limits access of pathogens to the epithelial surface.<sup>13</sup>

## Anti-inflammatory effect<sup>14</sup>

Gram-negative anaerobes are often implicated in secondary infections after abdominal surgery. The inhibitory effect of Lactobacillus plantarum 299v on Bacteroides was proven in a placebo-controlled study in patients with inactive ulcerative colitis.<sup>14</sup>

## Inhibition of pathogen colonization<sup>15,16</sup>

Enteral administration of Lactobacillus plantarum 299v to critically ill patients treated with antibiotics reduced colonization with C. difficile.<sup>15</sup>

When Lactobacillus plantarum 299v was consumed by children <5 years of age in a cereal-based fermented beverage, the proportion of children with isolated faecal enteropathogens decreased significantly ( $p < 0.001$ ) during the study period.<sup>16</sup>

## Inhibition of pathogen translocation<sup>17</sup>

Translocation is the passage of viable bacteria through the epithelial mucosa into the lamina propria and then to the mesenteric lymph nodes and possibly other tissues. It can be reduced by improving the status of the intestinal mucosa.

Experiments in rats with induced liver injury, which severely weakened the immune defence, allowed translocation of bacteria beyond the mesenteric lymph-nodes and the liver. However rats pre-treated with Lactobacillus plantarum 299v showed significantly decreased translocation.

Pre-treatment had a controlling impact on the intestinal microflora and enhanced the domination of Lactobacillus.<sup>17</sup>

## Decrease in gut permeability<sup>18,19,20,21</sup>

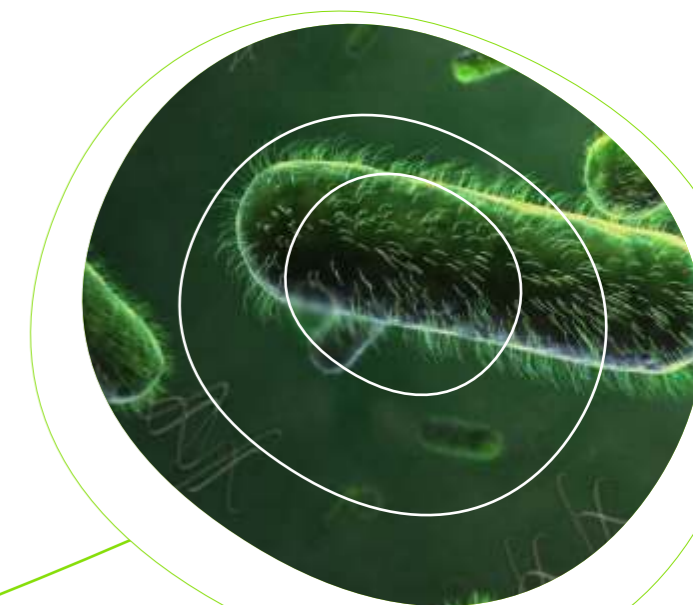
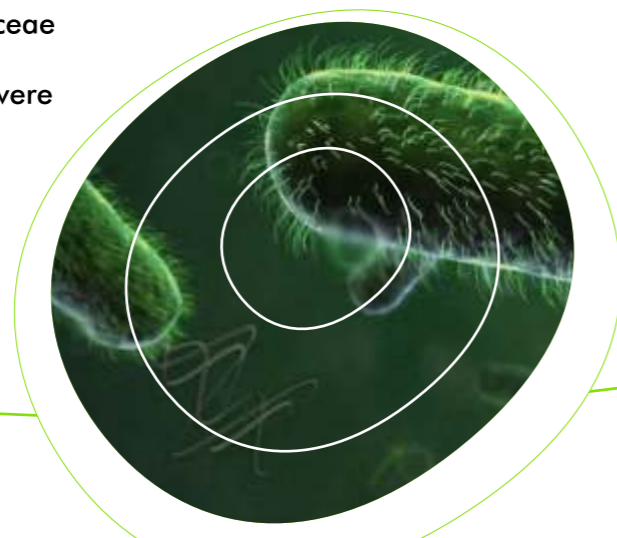
In rats with induced, acute liver injury, pre-treatment with Lactobacillus plantarum 299v improved their mucosal status and barrier function.<sup>18,19</sup>

There was a positive impact on gastrointestinal growth and function of suckling rats, when the lactating mother rats were fed Lactobacillus plantarum 299v. The small intestine, pancreas and liver weighed more in 14 day-old pups born of mother rats fed with Lactobacillus plantarum 299v, than in the control pups from mother rats fed on plain water. The Lactobacillus plantarum 299v pups showed decreased gut permeability.<sup>20</sup> Pups directly fed with Lp299v also displayed decreased gut permeability.<sup>21</sup>

## Rationale for protective mechanisms<sup>22, 23, 24, 25</sup>

Research has explained how Lactobacillus plantarum 299v improves the mucosal status and decreases the translocation rate of pathogenic bacteria.

- 1: colonization by lactobacilli which in turn inhibits growth of pathogenic bacteria.
- 2: the mannose sensitive adhesion-ability of Lactobacillus plantarum 299v that confers on it a translocation-blocking capability.<sup>22</sup>
- 3: the increase in overall bacterial diversity of the gut flora in humans after administration of Lactobacillus plantarum 299v.<sup>23</sup>
- 4: an improved barrier effect of the mucosa as a result of a beneficial immune-modulation and/or a stimulation of the mucin production of the human mucosa cells.<sup>24, 25</sup>



# PROBI:MAGE®

## HIGHWAY TO GOOD HEALTH

### Effect on Irritable Bowel Syndrome<sup>26,27,28</sup>

Lactobacillus plantarum 299v decreases the frequency and severity of IBS symptoms and often achieves complete remission in symptoms.<sup>26</sup>

The effects of Lactobacillus plantarum 299v on IBS were studied in a murine IBS model. Lactobacillus plantarum 299v reduced inflammation and normalized intestinal transit rates in the mice.<sup>27</sup>

Lactobacillus plantarum 299v was evaluated in IBS in two double blind, placebo controlled studies, in Poland<sup>26</sup> and in Sweden.<sup>28</sup> In the Polish study Lactobacillus plantarum 299v decreased the intensity of IBS symptoms with more patients becoming symptom-free.

In the Swedish study, Lactobacillus plantarum 299v significantly decreased bloating and pain.<sup>28</sup> Decrease in pain was more rapid and more pronounced in the Lactobacillus plantarum group. Also, Improved GI function in the Lactobacillus plantarum 299v group was evident a year after the study.

### Safety of Lactobacillus plantarum 299v<sup>29, 30, 31, 32, 33</sup>

Lactobacillus plantarum 299v is a natural resident of the healthy human gut. It is also found in many traditional lactic acid fermented foods that are consumed in many countries. Its reputation of being safe and wholesome is acquired from a long cultural tradition of consumption of such fermented foods.

The safety Lactobacillus plantarum 299v has been re-confirmed in clinical studies that concluded it was not translocated in abdominal surgery patients<sup>29</sup>; that it did not have adverse effects in immune-compromised children,<sup>30, 31</sup> or in critically-ill patients.<sup>32, 33</sup>

In summary, there are five characteristics of significance in Lactobacillus plantarum 299v. First, it moderates or completely reverses IBS and associated symptoms in humans; Second, it Inhibits intestinal adhesion of enteric bacteria; Third, it stimulates intestinal epithelial cells to produce mucin which inhibits bacterial adhesion; Fourth, it Inhibits growth of pathogens (in vitro); Fifth, it stimulates increase in intestinal count of lactobacilli.

### Description

Probi Digestis® contains Lactobacillus plantarum 299v, also called LP299V®, a single species of Lactobacillus that has a direct effect on human gastro-intestinal health.

Each vegetarian capsule of Probi Digestis® contains approximately 10 billion colony-forming units of Lactobacillus plantarum 299v (DSM 9843) at end of its shelf life.

### Indication

Probi Digestis® is indicated for reduction or elimination of signs and symptoms of Irritable Bowel Syndrome in adults.

### Dosage

The recommended dosage of Probi Digestis® in adults is 1 capsule/day. Probi Digestis® may be taken with or without food. While results with Probi Digestis® are generally quick, clinical studies have reported results within 4 weeks. Probi Digestis® can be taken concomitantly with other medications.





## LP299V® is effective in IBS – Here's proof.

### Clinical trial in India confirms Lactobacillus plantarum 299v improves symptoms of irritable bowel syndrome.

Ducrotte P, Sawant P and Venkataraman J: World Journal of Gastroenterology (2012); 18(30): 4012-4018

**AIM:** To assess the symptomatic efficacy of Lactobacillus plantarum 299v (L. plantarum 299v) (DSM 9843) for the relief of abdominal symptoms in a large subset of irritable bowel syndrome (IBS) patients fulfilling the Rome III criteria.

**STUDY DESIGN:** Double blind, placebo-controlled, parallel-designed study; subjects randomized to receive daily one capsule of Lactobacillus plantarum 299v (DSM 9843) or placebo for 4 weeks.

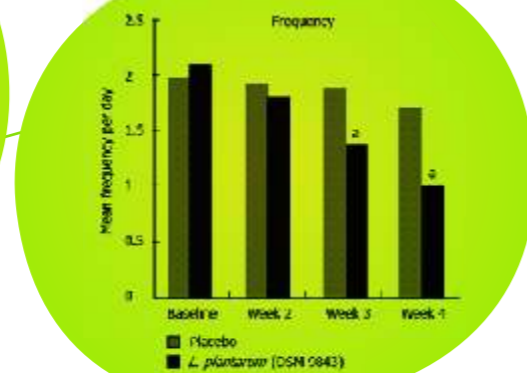
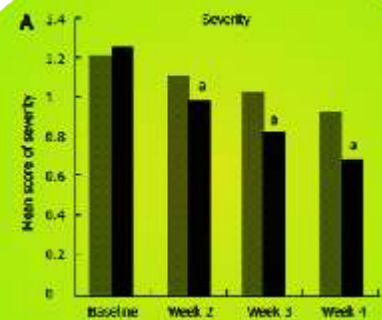
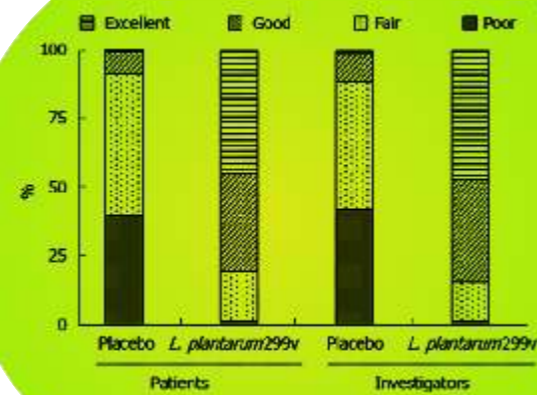
**RESULTS:** After 4 weeks, both pain severity (0.68 + 0.53 vs 0.92 + 0.57, P < 0.05) and daily frequency (1.01 + 0.77 vs 1.71 + 0.93, P < 0.05) were lower with Lactobacillus plantarum 299v than with placebo. Similar results were obtained for bloating. At week 4, 78.1 % of the patients scored the Lactobacillus plantarum 299v symptomatic effect as excellent or good v/s 8.1 % for placebo (P < 0.01).

**CONCLUSION:** A 4-week treatment with Lactobacillus plantarum 299v provided effective symptom relief, particularly of abdominal pain and bloating, in IBS patients fulfilling the Rome III criteria.

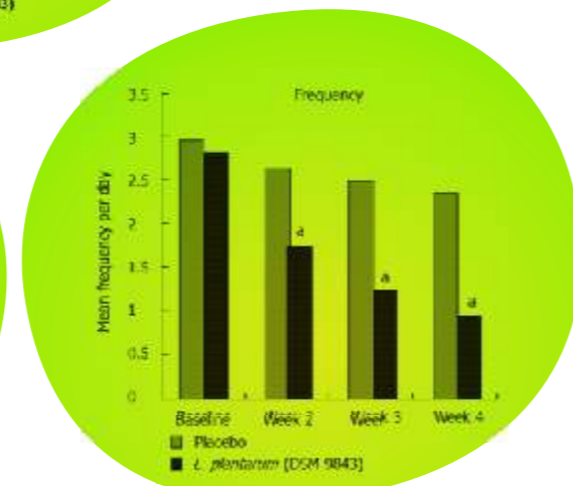
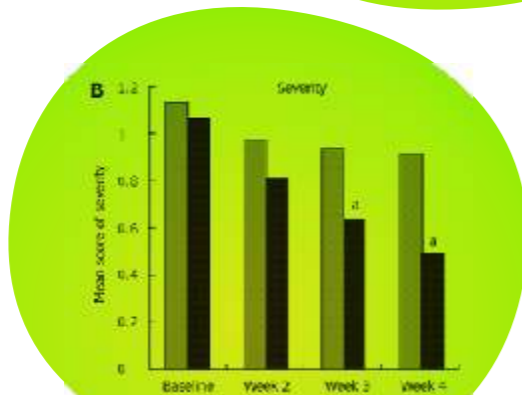
## Extracts from the India Study<sup>34</sup>

### Greater patient satisfaction<sup>34</sup>

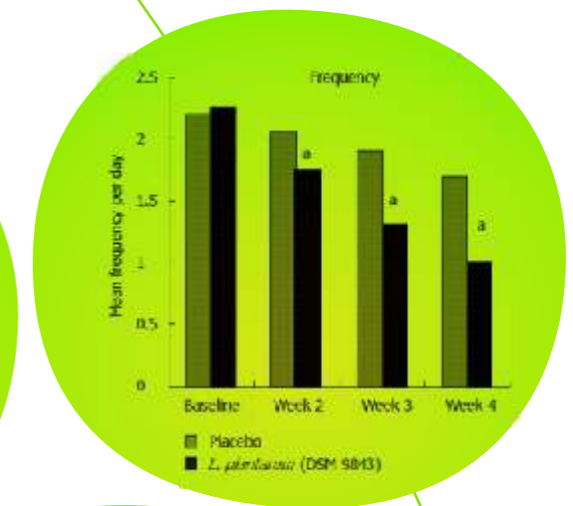
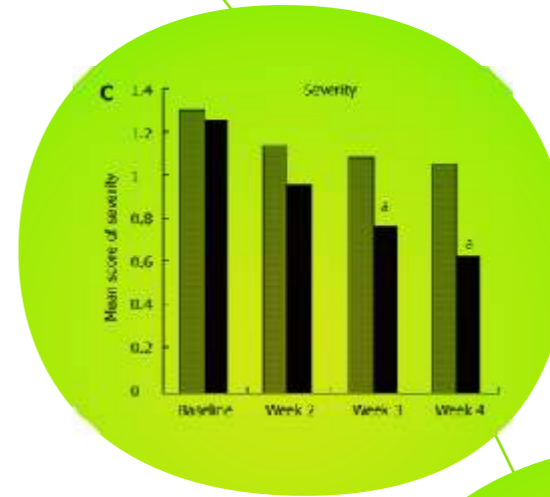
The percentage of patients who considered the efficacy of the treatment they received as good or excellent was significantly higher in the L. plantarum 299v (DSM 9843) group than in the placebo group (78.1% vs 8.1%) Similar results were observed when the efficacy was estimated by the investigators (82.8% vs 11.1%)<sup>34</sup>



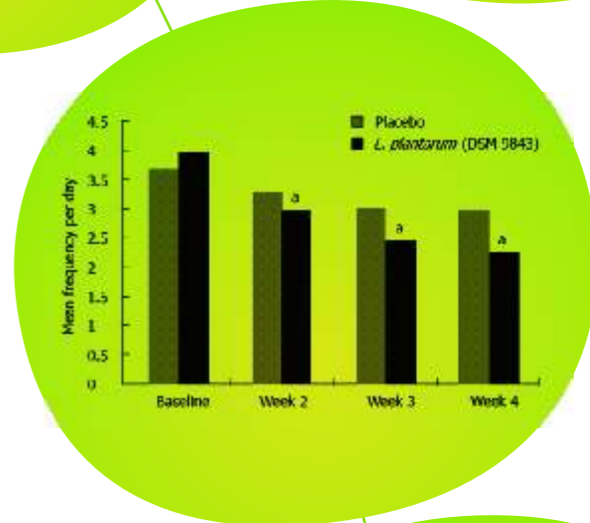
### Changes in Frequency and Severity of Bloating (αP < 0.05 vs Baseline)<sup>34</sup>



### Changes in Frequency and Severity of Feeling of Incomplete Evacuation (αP < 0.05 vs Baseline)<sup>34</sup>



### Changes in Frequency and Severity of Feeling of Incomplete Evacuation (αP < 0.05 vs Baseline)<sup>34</sup>



### Observations of other international researchers LP299V® reduces pain and flatulence

A significant decrease in abdominal pain was noted 1 week after the start of administration.<sup>26</sup>

Abdominal pain was rapidly reduced. Flatulence was rapidly and significantly reduced.<sup>28</sup>

### Better overall results\* compared to placebo (P < 0.0001)<sup>26</sup>

\*resolution of pain, constipation, diarrhea and flatulence.

### Proven ability to colonize, restore fecal flora and moderate symptoms<sup>26, 28, 35, 36</sup>

L. plantarum 299v survives low pH of the stomach, resists bile acids in duodenum and binds to the intestinal mucosa to colonize the gastrointestinal tract.<sup>26</sup>

Colonization by Lactobacillus plantarum causes a decrease in the colonic mucosa of bacterial groups with gas producing ability, such as clostridia.<sup>28</sup>

Survival of Lactobacillus plantarum 299v in the upper gastrointestinal tract enables its growth more distally in the system.<sup>35</sup>

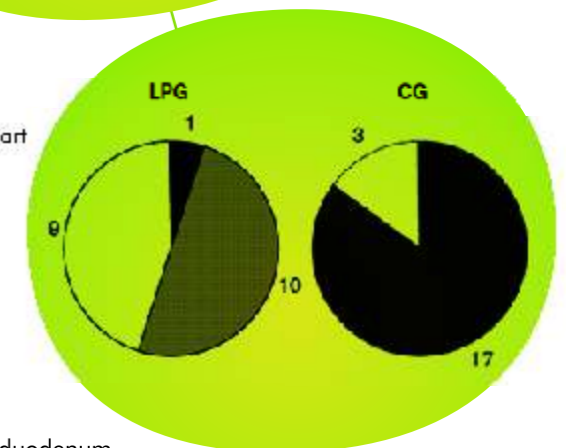
"After 3 weeks Lactobacillus plantarum 299v was found in the faeces of all children except one and in none in the placebo group."<sup>36</sup>

### Reduces level of pathogenic intestinal flora<sup>36</sup>

Intake of Lactobacillus plantarum 299v reduces the presence of potential pathogenic bacteria in intestinal flora.<sup>36</sup>

### After 1 year, LP299V continues to demonstrate its effect<sup>28</sup>

At the 12-month follow-up patients in the LP299V® group still had a significantly better function compared to baseline, whereas those in the placebo group did not.<sup>28</sup>



Comparison of the effect of Lactobacillus plantarum 299v and placebo after 4 weeks of treatment. LPG, Lactobacillus plantarum 299v group; CG, control group. (■), No improvement; (□), partial improvement; (□), complete reduction of IBS symptoms.