



## Human, *In Vitro* and *In Vivo* Studies on EpiCor®'s Gut Health Effects



**Summary:** The digestive system and gut microbiome are essential for many aspects of proper human health including immunity, digestive function, digestive comfort and more. EpiCor fermentate's benefits on gastrointestinal health and microbial modulation have been demonstrated by several published human, *in vitro* and *in vivo* trials. These studies include a human clinical trial on digestive comfort and microbiome modulation<sup>1</sup>, studies using various sophisticated *in vitro* gut models<sup>2,3</sup>, a gut epithelium human model<sup>4</sup> and a gut wall integrity animal model<sup>5</sup>.

The goal of this scientific summary is to show the three key ways EpiCor effects gut health:

### 1. Gut Microbiome Modulation/Prebiotic Effects:

- Beneficially modulates the population of the gut microbiota which includes reducing the Firmicutes and Bacteroidetes ratio<sup>1,2,3</sup>. **(Human and *in vitro*)**
- Alters both the luminal population of bacteria and the population bound to a modeled gut wall<sup>3</sup>. **(*In vitro*)**
- Increases Short Chain Fatty Acid (SCFA) production – especially butyrate – compared to a cellulose control<sup>2,3</sup>. **(*In vitro*)**

### 2. Gut Wall Integrity and Inflammation:

- Protects gut wall integrity from heat stress<sup>5</sup>. **(*In vivo*)**
- Decreases pro-inflammatory markers<sup>3</sup>. **(*In vitro*)**
- Reduces histamine-induced inflammation using skin as a model for gut intestinal lining<sup>5</sup>. **(Human)**
- Stimulates salivary secretory immunoglobulin A (sIgA)<sup>5,6</sup>. **(Human)**

### 3. Digestive Comfort, Constipation and Quality of Life

- Significantly provides relief to those with mild digestive discomfort by reducing bloating and feelings of fullness within two weeks<sup>1</sup>. **(Human)**
- Significantly improves stool consistency within two weeks<sup>1</sup>. **(Human)**



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## Introduction

The majority of published research on EpiCor fermentate has shown support, activation and modulation of various aspects of the immune system to positively impact health<sup>3,4,6,7,8,9,10</sup>. These studies demonstrate EpiCor's mechanisms of action in strengthening the immune system and reveal some biochemical immune markers that are linked to the digestive system. Due to well-established interactions that occur between the immune system and the digestive system, it seemed likely that EpiCor would positively affect gut health as well. This led Embria to undertake several studies to assay EpiCor's benefits on the gut microbiome, gastrointestinal (GI) mucosal lining and digestive function.

This white paper summarizes five published EpiCor studies referenced as:

1. Human clinical study on subjects with mild constipation
2. Simulator of the Human Intestinal Microbial Ecosystem (SHIME®)
3. Host-Microbiota Interaction (HMI)
4. Heat-stress animal model on gut integrity
5. Epithelial inflammation model

## Prebiotic Effects: Microbiome Modulation

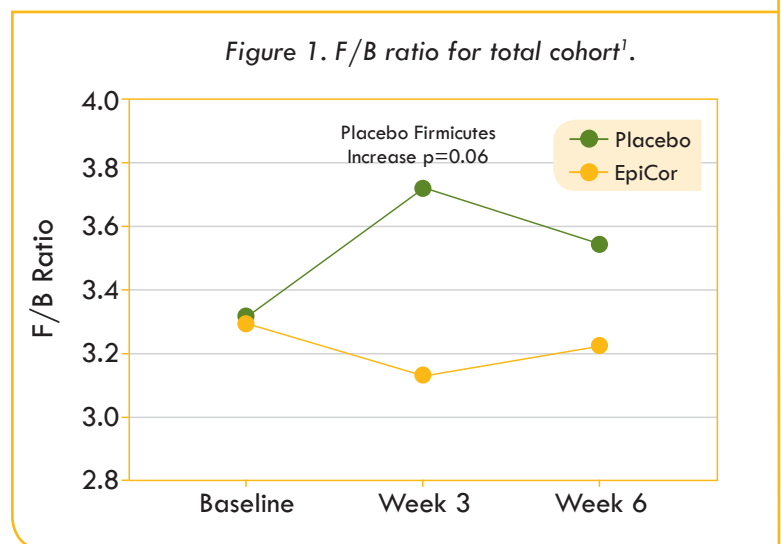
**Human clinical study on subjects with mild constipation.** One of the benchmarks for prebiotic activity is beneficial effects on the microbiotic environment of the digestive tract, otherwise known as the microbiome. Microbiome modulation by EpiCor was shown in humans in a double-blind placebo-controlled clinical trial<sup>1</sup>. The subjects of this study experienced non-medically treated constipation and were subdivided into two groups: those suffering from mild discomfort and those suffering from severe discomfort. The primary outcome for this study was assaying EpiCor's effect on digestive discomfort. These results and discussion on the two subgroups will be discussed later in this summary.

The gut microbiota assay was done on a subset of 80 subjects by analyzing fecal samples taken before treatment with either EpiCor (500mg/day) or placebo before treatment (baseline), after three weeks, and after six weeks of treatment. Genetic sequencing revealed changes in certain bacterial groups during the course of treatment.

The statistically significant changes over time from baseline with EpiCor treatment are as follows (in each case the corresponding placebo group either did not see a significant change or saw an opposing change):

- **Firmicutes/Bacteroidetes (F/B) ratio decreased** compared to placebo in the entire cohort (Fig 1)<sup>1</sup>. A high F/B ratio is associated with constipation. In a previous study, a two-fold increase in the F/B ratio had been found in patients with irritable bowel syndrome with constipation (IBS-C) when compared to healthy individuals<sup>11</sup>.

- **Anaerostipes increased** in the entire cohort. *Anaerostipes* is a genus recognized for its health enhancing effects and contains butyrate-producing bacteria as well as acetate- and lactate-consuming bacteria<sup>12</sup>. The importance of producing butyrate will be discussed later in this summary.



- **Akkermansia muciniphila increased** in those suffering from mild discomfort<sup>1</sup>. *Akkermansia muciniphila* is important for proper gut function and is inversely correlated with metabolic disorders<sup>13</sup>.
- **Blautia and Roseburia decreased** in those suffering from mild discomfort<sup>1</sup>. *Blautia* and *Roseburia* are believed to be higher in irritable bowel syndrome (IBS) and those suffering from IBS-C<sup>11</sup>.
- **Prevotella increased** in those suffering from severe discomfort<sup>1</sup>. A lower incidence of species in the Prevotellaceae family has been associated with low-fiber diets and insufficient plant-based food consumption<sup>11,14</sup>, which is a major cause of dysbiosis in constipated patients<sup>15</sup>.
- **Bacteroides increased** in those suffering from severe discomfort<sup>1</sup>. The increase in *Bacteroides*, a part of the Bacteroidaceae family, may help explain EpiCor's positive effects on stool frequency and consistency mentioned later in this summary.

**SHIME Study.** EpiCor treatment was also studied in a sophisticated *in vitro* digestive system model called the SHIME. The research on EpiCor was conducted by ProDigest, a Belgian research organization that is associated with the University of Ghent that developed the SHIME model. The system is designed to screen treatments for prebiotic and probiotic activity and can assay effects that are not possible to study in a human trial.

SHIME uses a series of connected vessels each representing a different part of the digestive tract (Fig. 2)<sup>2</sup>. Analogs of food and the appropriate digestive solutions (enzymes, bile salts, etc.) are added to the vessels that represent the stomach, small intestine and the three parts of the colon. A treatment, such as EpiCor or a control substance, can be tested by adding it to the first vessel (stomach). An established human gut flora inoculum (*i.e.* a complete culture of micro-organisms sampled from a specific person's digestive tract) is added to the vessel representing the ascending colon (*i.e.* the first section of the large intestine). The microflora and its metabolites are then assayed while food and treatment are run through the system over weeks.

Using the SHIME, EpiCor treatment increased the levels of Bifidobacteria and Lactobacilli bacterial groups as compared to the cellulose control (Fig. 3)<sup>2</sup>. Bifidobacteria and Lactobacilli help the gut break down food and stave off disruptive bacteria. These results show that EpiCor is comparable to inulin and FOS in the prebiotic effect of modulating the gut microflora.

Figure 2. Illustration of the SHIME model courtesy of ProDigest<sup>2</sup>.

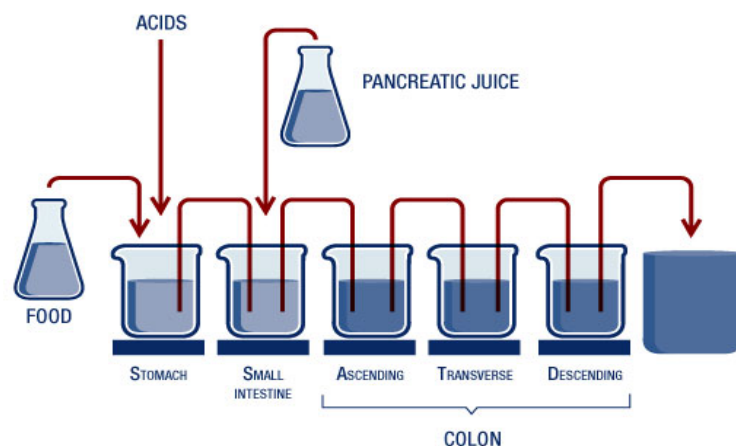
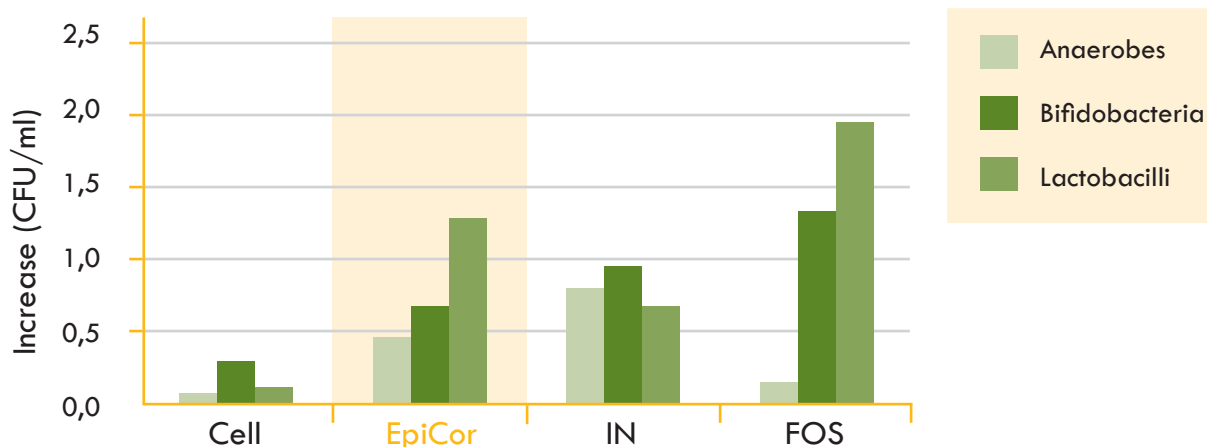


Figure 3. The Effect of EpiCor on Bacterial Populations in the SHIME<sup>2</sup>. This graph shows the increase of bacterial population density in colony forming units (CFU) per milliliter using the SHIME digestive system model. The four treatments are cellulose (Cell), EpiCor, inulin (IN) and fructo-oligosaccharides (FOS).



**HMI Study.** Further experiments with ProDigest utilized the HMI Module<sup>3</sup>. This is a flowing system where the microbiota is passed over a layer of cells simulating the gut cell wall. The results demonstrate that EpiCor modifies which bacteria adhere to the simulated gastric wall. It showed a trend for increased adherence of Lactobacilli species and a trend for decreased adherence of Clostridia species.

### Prebiotic Effects: Short Chain Fatty Acid Production

Short chain fatty acids (SCFAs) produced by bacteria during digestion have been recognized for many years as sources of energy for the host. The SCFAs are mainly derived from fermentation reactions in the distal sections of the digestive system<sup>16</sup>. Recently, there has been considerable interest in the effects of SCFAs, in particular butyrate, on immune health. Apart from butyrate's association with energy, it is thought to interact directly with parts of the immune and digestive systems. Research has shown butyrate's beneficial effects on the structure of the gut wall and on its ability to alter cytokine profiles in such a way that the immune response is modulated. The effects include increasing levels of interleukin 10 (IL-10), an anti-inflammatory cytokine<sup>17</sup>.

Increases in SCFA production is another hallmark of a prebiotic effect since it indicates that the microbiome is being modulated in such a way that fiber is being converted more efficiently into usable energy sources.

**SHIME Study.** The SHIME system is an excellent way to assay how various treatments can alter the SCFA production by gut microflora. Using SHIME, EpiCor caused an increase in total SCFAs compared to a control<sup>2</sup>. This increase was comparable to increases seen with inulin or FOS treatment. Moreover, EpiCor shifted the pattern of SCFA to produce more butyrate (significant in the comparison of EpiCor to FOS,  $p < 0.05$ )<sup>2</sup> (Table 1). This occurred despite EpiCor providing relatively miniscule levels of fiber, which is also why EpiCor is not associated with the side effects common with prebiotic fibers.

Table 1. The effect of EpiCor on the percent increase SCFAs over baseline<sup>2</sup>.

	EpiCor	Inulin	FOS
Acetate (%)	48	57	64
Propionate (%)	30	30	26
Butyrate (%)	21	14	9

### Gut Wall Integrity and Inflammation

An important function of the GI tract is to provide a barrier between the gut environment and the rest of the body. Dysfunction in this role results in the leaking of bacterial toxins into the blood stream, which can then result in a dangerous immune response.

Figure 4. Villus height<sup>5</sup>.

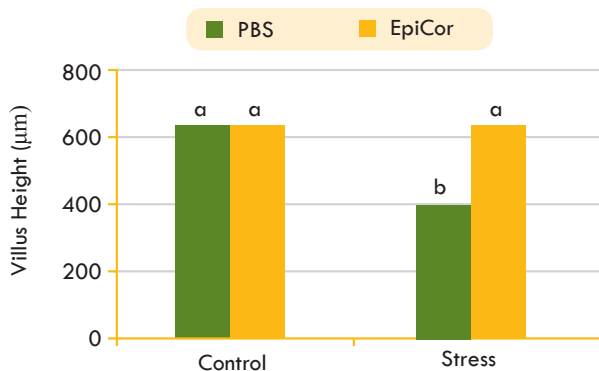
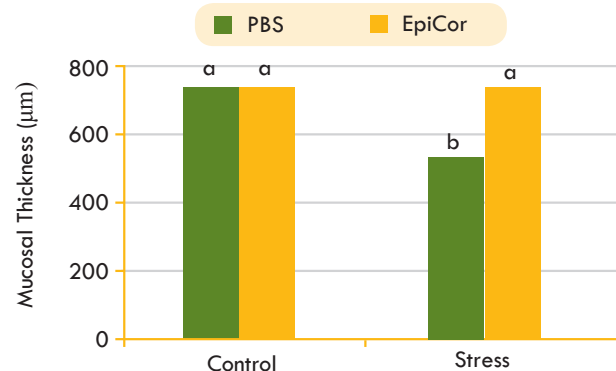


Figure 5. Mucosal Thickness<sup>5</sup>.



**Heat-stress animal model on gut integrity.** To determine whether EpiCor treatment can assist in shoring up this barrier, a heat-stress model in rodents was used<sup>5</sup>. Rats were fed either EpiCor (7 mg/kg body weight/day, which is equivalent to a 500 mg/day dose in an adult human) or a placebo. Half of each group were then put under heat stress at 45°C (113°F) for 25 minutes.

Along the gut lining, villus height and mucosal thickness both decreased in heat-stressed placebo-treated rats versus the rats that were not heat-stressed ( $p < 0.05$ ). However, the heat-stressed rats fed EpiCor showed no adverse changes in these gut integrity parameters (Fig. 4-5)<sup>5</sup>.

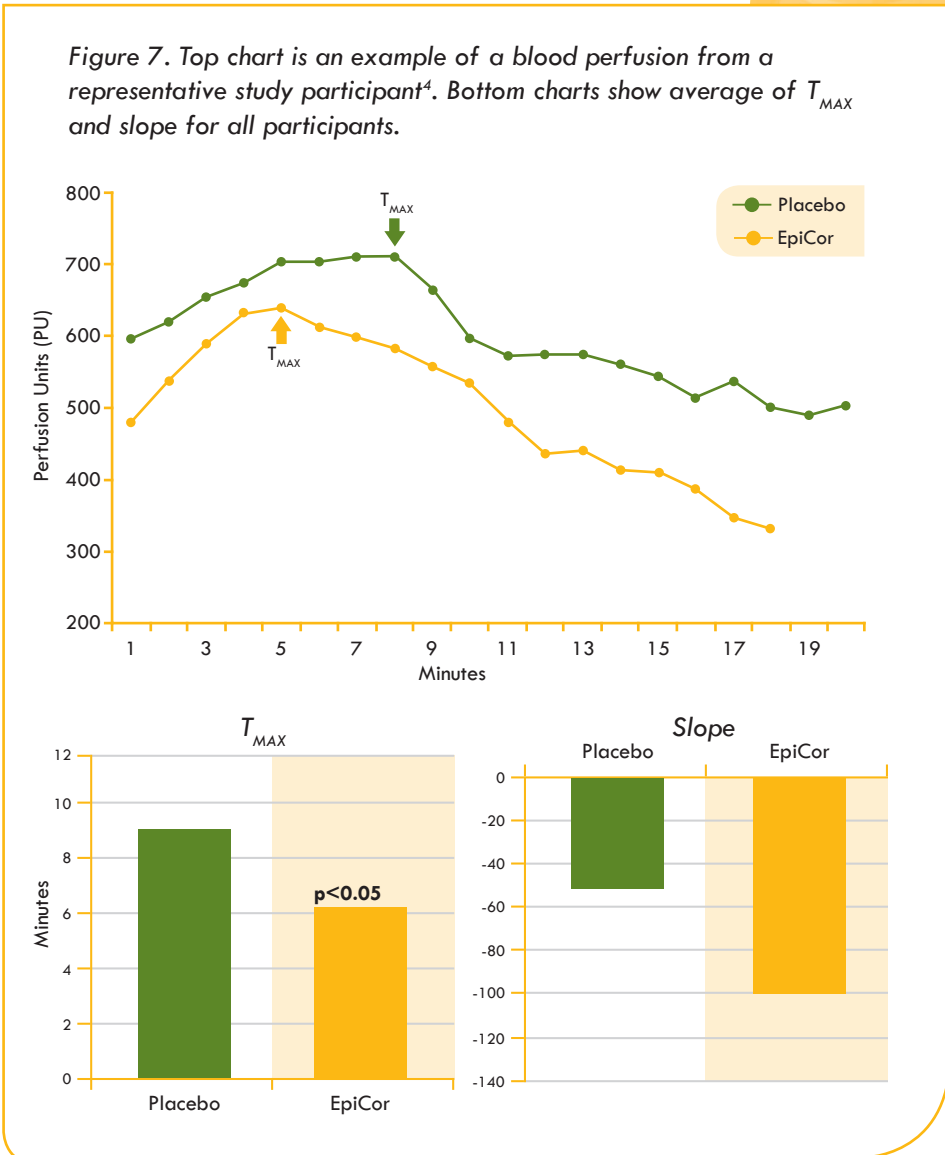
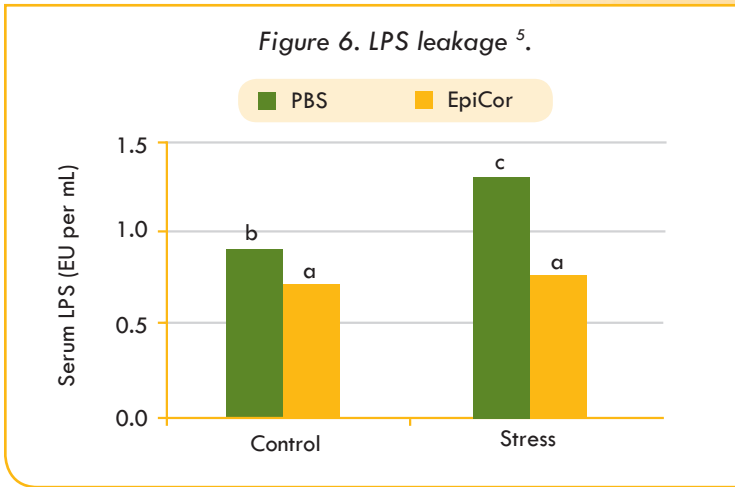
To test how permeable the gut gets under heat-stress, lipopolysaccharide (LPS), a bacterial endotoxin, was measured in the serum. Although LPS is safe within the gut, poor gut wall integrity allows it to enter the bloodstream. Heat-stressed placebo-treated rats had significantly more LPS leak through the gut wall and reach the bloodstream than the non-heat-stressed rats, indicating that heat-stress causes higher permeability (Fig. 6)<sup>5</sup>. However, the EpiCor-treated heat-stressed rats showed no increase in serum LPS. Moreover, the EpiCor-treated rats showed improved gut integrity (as measured by serum LPS) even over rats that did not go through heat stress.

This research suggests that regular consumption of EpiCor is capable of mitigating certain damage to the surface layer of the gut and associated toxin leakage into the blood stream.

### Anti-Inflammatory Effects of EpiCor in the Gut

Inflammation in the gut occurs naturally for most people. If left unchecked it can lead to various problems. The ability to reduce inflammation in the GI system and gut mucosal lining would be a key factor in proving effectiveness of EpiCor on maintaining gut health. Previous research on animals has demonstrated general anti-inflammatory effects of EpiCor ingestion<sup>18</sup>. These results prompted a human clinical study using controlled inflammation of the epidermis as a model for the gut lining<sup>5</sup>.

**Epithelial inflammation model.** The skin of each arm of 12 participants was scratched and then coated with histamine, to cause inflammation<sup>4</sup>. After one minute, one scratch was then coated with a control of saline solution while the scratch on the other arm was coated with an EpiCor saline solution. The inflammatory response was monitored



by the initial increase of sub-cutaneous blood flow, followed by the subsequent decrease of flow as it returned to the baseline level.

Both the time taken to reach the maximum response in terms of blood flow ( $T_{MAX}$ ) and the time taken for the increased blood flow to return to baseline (measured as the slope of the decrease in blood flow) are relevant to the inflammatory response. The return to baseline is termed the resolution of the inflammatory response.

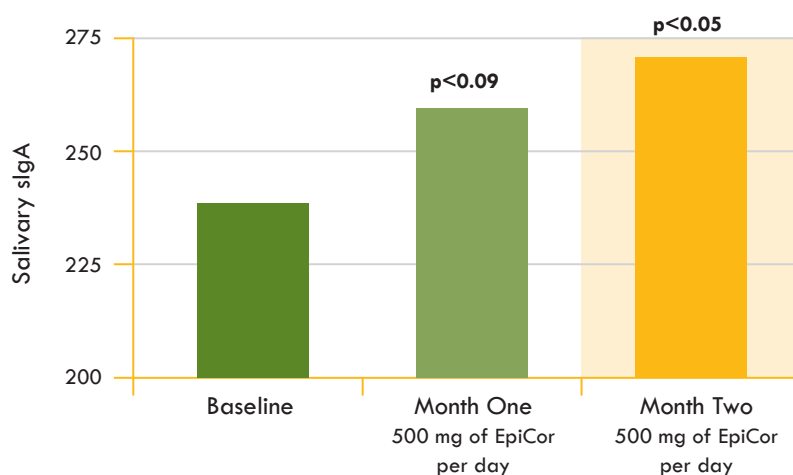
Clinical results demonstrated significantly reduced microvascular inflammatory responses to histamine-induced skin inflammation and significantly reduced subjective scores of irritation at the inflamed sites treated with EpiCor compared with the sites treated with placebo ( $p < .05$ ). The arm with the added EpiCor extract showed a faster resolution of the inflammation – the peak blood flow was reached over two minutes sooner than the control (Fig. 7)<sup>4</sup>. Also the recovery to the baseline level was faster (Fig. 7)<sup>4</sup>. In both cases the difference was statistically significant ( $p < .05$ ).

**HMI model.** Epithelial inflammation was also tested using the SHIME and HMI models discussed previously. Bacterial populations cultured in the SHIME model were sampled at different time points during EpiCor treatment<sup>3</sup>. These populations were then run over a layer of epithelial cells simulating the gut wall. Results showed that the longer the microbiota was treated with EpiCor, the fewer inflammatory markers the epithelial cells produced.

### Salivary sIgA Antibodies

Research has shown that one of the immune markers EpiCor significantly increases is secretory immunoglobulin A (sIgA) antibodies found in saliva<sup>6,7</sup>. This antibody can be found throughout the mucosal system and most importantly in the Gut-Associated Lymphoid Tissue (GALT). The GALT is the main interface between the immune and digestive systems and helps prevent infections and invasions through the gut lining.

Figure 8. EpiCor effects on salivary sIgA<sup>6</sup>.



It is known that sIgA plays a crucial role in the GALT: the amount of IgA produced in the mucosal barrier is greater than all other antibodies combined. It is a key antibody in the first line of defense in protecting the intestinal epithelium from enteric toxins and pathogenic microorganisms<sup>19</sup>.

Human clinical trials have shown that EpiCor helps significantly increase levels of salivary sIgA versus placebo<sup>6,7</sup> (Fig. 8). Embria is extrapolating salivary sIgA results to what would be anticipated for sIgA results within the gut. EpiCor's ability to increase sIgA within the gut has never been researched in humans. To test for sIgA within the gut, the procedure would be invasive and possibly harmful. sIgA can be produced in a variety of ways, but the

predominant method is via the Peyer's Patches in the GALT. With EpiCor taken orally in studies and absorbed through the gut, it can be inferred that increases shown in salivary sIgA might mean increases in sIgA in the gut.

### Digestive Discomfort, Constipation and Quality of Life

**Human clinical study on subjects with mild constipation.** Using a double-blinded, placebo-controlled parallel design, 80 healthy subjects with symptoms of GI discomfort and constipation were either treated with placebo or EpiCor (500 mg/day)<sup>1</sup>. Randomization was done in a stratified manner

according to symptom severity, resulting in two subgroups of patients: severe discomfort (n=55) and moderate discomfort(n=25).

The instrument that was used to assess severity was a validated gastrointestinal (GI) discomfort diary. It asked subjects to record the extent of five GI symptoms: bloating/distention, gas, GI rumbling, feeling of fullness and abdominal discomfort. All symptoms were assessed on a five-point scale: 0 (absent) to 4 (very severe). Combining the scores gives a daily total score (DTS).

Within the first two weeks, the moderate subgroup taking EpiCor showed rapid and statistically significant improvements for gastrointestinal discomfort when compared to the corresponding placebo group. Along of with the total score (DTS), two specific GI symptoms by themselves showed improvement compared to placebo ( $p \leq 0.05$ ): bloating and feelings of fullness (Fig. 9-10)<sup>1</sup>. This finding is especially notable because bloating and fullness are often exacerbated by treatment with fiber-based prebiotics. Improvement over time was also seen in the EpiCor-treated severe subgroup and total cohort with some time points reaching statistical significance compared to baseline ( $p \leq 0.05$ ). However, significance compared to placebo was not reached due to a noticeable placebo effect that increased over time. It is well established that placebo effect is common for gut-related trials with gastrointestinal disorders such as functional constipation<sup>20,21,22,23</sup>. This suggests why the placebo effect was generally more pronounced in the severe group.

Significant improvements in stool consistency (assessed using the Bristol Stool Form Scale) were seen in both the EpiCor total cohort group and the severe subgroup compared to corresponding placebo groups. The improvements were seen at week two, showing both a rapid and significant response to EpiCor (Fig. 11)<sup>1</sup>. Consistency also improved with significance over time for the EpiCor-treated moderate group but improvement compared to placebo to not reach significance for this group.

A significant improvement in stool frequency compared to baseline was seen in EpiCor moderate subgroup but not in the corresponding placebo subgroup. A trend toward improvement for stool frequency was seen in weeks two and four in the EpiCor total cohort as compared to placebo ( $p < 0.10$ ).

## Discussion

The results summarized in this paper show that EpiCor has substantiated gastrointestinal benefits. The digestive health category is currently dominated by probiotics. EpiCor whole food fermentate is a new and novel approach that can help companies differentiate their gut

Figure 9. Bloating/distension: moderate group.

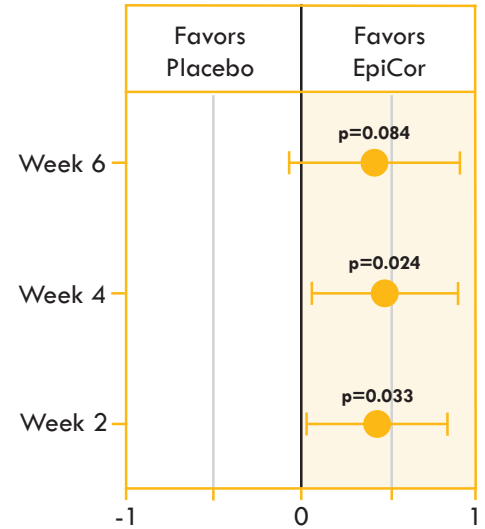


Figure 10. Feeling of fullness: moderate group.

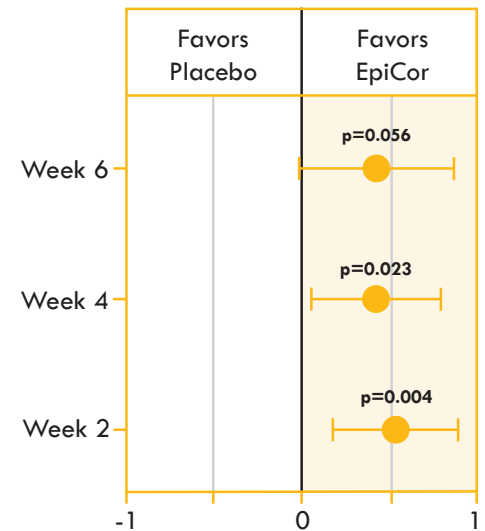
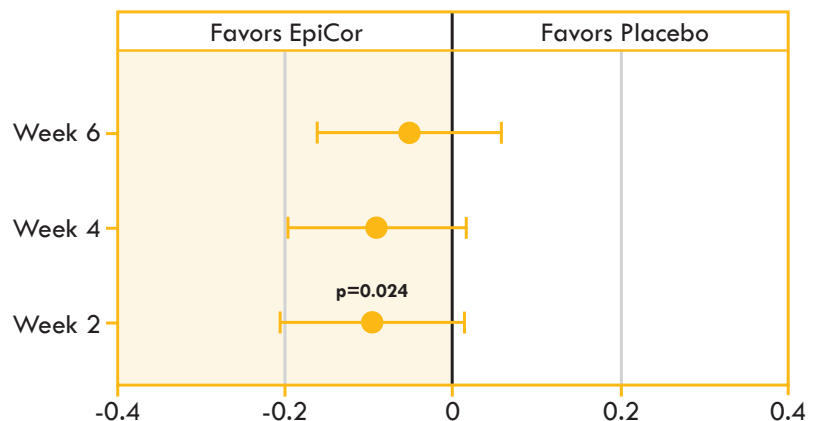


Figure 11. Stool consistency: total cohort<sup>1</sup>. This chart shows the mean differences between EpiCor and placebo on gastrointestinal symptoms (as recorded on a daily basis by self-assessment using the Bristol Stool Form Scale), analyzed with a linear mixed model that takes into account the differences between groups at baseline.



health offerings. EpiCor's prebiotic effects open up the ability to create synbiotic products because of its low efficacious dose. EpiCor's digestive health benefits along with clinically shown immune benefits make it an advanced solution in the gut health category.

EpiCor was developed to support immune health due to a surprising discovery: workers at a fermentation plant took less sick days than their office worker counterparts. This led to a series of studies showing the wide extent of EpiCor's role in immune health, including seven published human clinical trials. Concurrently, assays on EpiCor's mode of action indicated that EpiCor treatment may have effects in the gut, including decreasing inflammatory markers and increasing salivary secretory IgA (IgA is the most abundant antibody in the human mucosal layer). This led Embria to undertake studies that specifically assayed EpiCor's effect on gut function and health.

It is now increasingly understood that digestive health is highly dependent on the gut's microbiome, the microbiotic environment living in our digestive tract. Many digestive supplements are geared toward attempting to modify the microbiome for the better. For example, many probiotic supplements contain Lactobacilli and Bifidobacteria, which are both considered beneficial organisms in that they help "exclude" pathogenic bacteria, thus reducing the possibility of disease and other digestive problems. Thus, EpiCor's first digestive health studies used a gut model system to specifically look at microbiome population shifts and indeed saw increases in Lactobacilli and Bifidobacteria.

Unlike probiotics, EpiCor is a whole food fermentate and not "alive". The *Saccharomyces cerevisiae* that is used to make EpiCor is completely inactive and comprises just part of its metabolite-rich composition. Probiotics aim to supplant the gut with new bacteria, whereas it appears that EpiCor is stimulating the human gut's endogenous beneficial bacteria. This was seen in the model studies and in a human clinical trial. In this aspect, EpiCor is more comparable to prebiotics, which are defined as substrates that are selectively utilized by host microbiota to give health benefits<sup>24</sup>. Although, EpiCor does have prebiotics effects, it not a prebiotic fiber. Prebiotic fibers are known to be a good food source for the bacteria, but their digestion in the gut can lead to bloating and gas. Prebiotic fibers also require doses of several grams to be effective could make it hard to formulate into small delivery forms such as capsules, gummies, chews, lozenges and more.

EpiCor has many advantages and differences from prebiotic fibers including:

- No side effects while providing significant reduction of bloating for those with mild constipation
- Significantly provides relief to those with mild digestive discomfort within two weeks
- Significantly improves stool quality
- Fermentation occurs outside the gut and thus does not cause gas when ingested
- Clinically shown immune health benefits in hundreds of subjects with a consistent dose
- Relatively low efficacious dose of 500mg

Another important prebiotic effect is stimulating the conversion of dietary fiber into SCFAs. Short chain fatty acids are an instrumental energy source to the cells that line the gut. EpiCor treatment showed SCFA production comparable to the effects seen using fiber-based prebiotics. The combination of the prebiotic effects shown in laboratory models and the beneficial modulation of bacterial groups seen in a human clinical study suggest that daily consumption of EpiCor may help balance the gut flora and provide the energy needed for healthy gut lining function.

So are there specific benefits to the gut lining occurring with EpiCor treatment? To test this, a heat-stress animal model was deployed and indeed the EpiCor treatment mitigated the detrimental effects that heat-stress caused on the gut lining including decreases in mucosal thickness and increases in permeability, as measured by endotoxin leakage into the blood. In fact, even without stress, EpiCor treatment resulted in less gut permeability than a placebo group. Another important indicator of a healthy gut epithelium (the "skin" of the gut lining) is reduced inflammation. Inflammation in the gut is a normal immune response, but long term and sub-clinical inflammation can cause both transient and chronic damage to the individual. In studies modeling the cells lining the gut, inflammation and pro-



inflammatory markers were seen to decrease due to EpiCor treatment.

These mode of action findings indicate EpiCor treatment should have clinically relevant results on human digestive health. Indeed, in a randomized placebo-controlled clinical trial, EpiCor led to statistically significant improvements in symptoms such as bloating/distension and feelings of fullness in subjects with moderate digestive discomfort. Such improvements offer a compelling advantage for EpiCor over prebiotic fibers, which are known to increase GI discomfort at efficacious dose levels.

The gastrointestinal system is very complex and these studies show that EpiCor helps improve GI health by working intricately within the digestive system. Only with more studies on EpiCor will Embria understand all the aspects of how it beneficially effects digestive function.

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