Phase I Randomized Controlled Study of a Single-Strain Live Biotherapeutic (*BLAUTIA HYDROGENOTROPHICA*) in the Treatment of Patients with Irritable Bowel Syndrome (IBS) : Effects on the Microbiome

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4D pharma plc is a pharmaceutical company focused on developing therapeutics from the human gut microbiome. Live biotherapeutic products (LBPs) derived from the gut microbiome represent a new class of drugs that contain live organisms for the prevention, treatment or cure of disease. 4D Pharma is a world leader in the LBP field and currently has two clinical stage programmes (in IBS and IBD) and a strong pipeline of pre-clinical programmes in autoimmunity, inflammation, oncology and CNS disease.

Background

- Alterations in the gut microbiota are increasingly being implicated as potential etiological factors giving rise to an emerging field of research focused on the therapeutic manipulation of the microbiome using live bacteria to improve symptoms of IBS.
- Blautix™ (BHT) is a live biotherapeutic product under development for the treatment of IBS.
- The active ingredient of BHT is a strain of the bacterium *Blautia hydrogenotrophica* (*B. hydro*) lyophilized and formulated as gastro-resistant enteric capsules for oral administration.
- B. hydro is a gram-positive, anaerobic, non-sporulating, coccobacillus bacterium that is commensal in the human gastrointestinal tract.
- The mode of action of BHT is believed to be due at least in part to its ability to restore the gut microbiota to a health associated functional composition which may play an important role in alleviating IBS-related symptoms.

Objectives

- To assess the safety and tolerability of BHT given as repeated oral doses to subjects with and without symptoms of IBS compared to placebo;
- Explore the effects of BHT on the microbiota of healthy subjects with and without IBS symptoms based on the following parameters:
  - Stability
  - Diversity
  - Global microbiota profile
- Assess the intensity of IBS symptom change.

Study Design and Methods

- A double-blind placebo-controlled Phase 1 study was conducted on 48 subjects.
- Subjects with and without symptoms of IBS received BHT or placebo in a 2:1 ratio.
- Twice daily doses of >10^{10} CFU of BHT or placebo were administered over 2 weeks, followed by a 2-4 week washout period.
- Fecal samples were collected at baseline (Day 1), at the end of treatment (Day 16) and again 2-4 weeks later (EOS) and were analyzed using qPCR for the presence of BHT and for microbiota composition.

Table 1. Baseline Characteristics

	Subjects without IBS	Subjects with IBS	
Age Years, mean ± SD Range	28.6 ± 9.03 19 – 50	28.0 ± 7.31 20 – 47	
Sex (N) Male Female	14 16	7 20	
Treatment Abdominal Pain and Discomfort Bloating Constipation Diarrhea		Placebo (N=10) 10 10 8 9	BHT (N=17) 16 16 9 14

Table 2. Summary of Adverse Events

	Healthy Subjects		IBS Subjects	
Treatment (N)	Placebo 10	BHT 17	Placebo 10	BHT 17
No. of Treatment AEs, AEs/N	15/6	14/6	11/7	21/10
Gastrointestinal Disorders	12/6	10/6	10/6	18/9
Abdominal Distention			1/1	8/5
Abdominal pain upper		1/1		5/5
Abdominal pain	6/4		5/4	
Constipation		1/1		
Diarrhea		2/2	2/1	2/2
Feces Soft		1/1		
Flatulence	4/2	3/2	1/1	1/1
Nausea	2/2	1/1	1/1	2/2
Vomiting		1/1		
General Disorders	3/1			
Fatigue	3/1			
Hepatobiliary Disorders			1/1	1/1
Hyperbilirubinemia			1/1	1/1
Infections		1/1		
Nasopharyngitis		1/1		
Nervous System Disorders		3/3		2/1
Headache		2/2		2/1
Hypogeusia		1/1		

Table 3. IBS Symptom Change

	Placebo N (%)	BHT N (%)
Improving	5 (50)	14(82)
Worsening	3 (30)	2 (12)
No Change	2 (20)	1 (6)

Results

- There were 57 subjects in the study and groups were homogeneous except for 75% females with IBS symptoms (Table 1).
- Repeated oral doses of BHT were well tolerated. No differences were observed in in the AEs observed between subjects with and without symptoms of IBS (Table 2).
- More IBS subjects who received BHT (82%) showed an improvement in symptom scores compared to placebo subjects (50%), with improvement seen in pain/discomfort/cramps, bloating and diarrhea scores (Table 3).
- Microbiota change in diversity (Figure 1) shows the majority of subjects in the Healthy BHT group clustered around 0, similar to the Healthy placebo group, while most of the IBS BHT treated group have a value > 0. A reduction in the diversity of the IBS placebo group over the treatment period was observed but was not significant.
- Analysis of the Bray-Curtis dissimilarity metric showed that BHT treatment reduced the level of instability/change of species in the microbiota in IBS subjects during the course of study (Figure 2). The stability of microbiota in patients on BHT was comparable to that of the healthy controls.

Figure 1. Effect on Microbiota Diversity

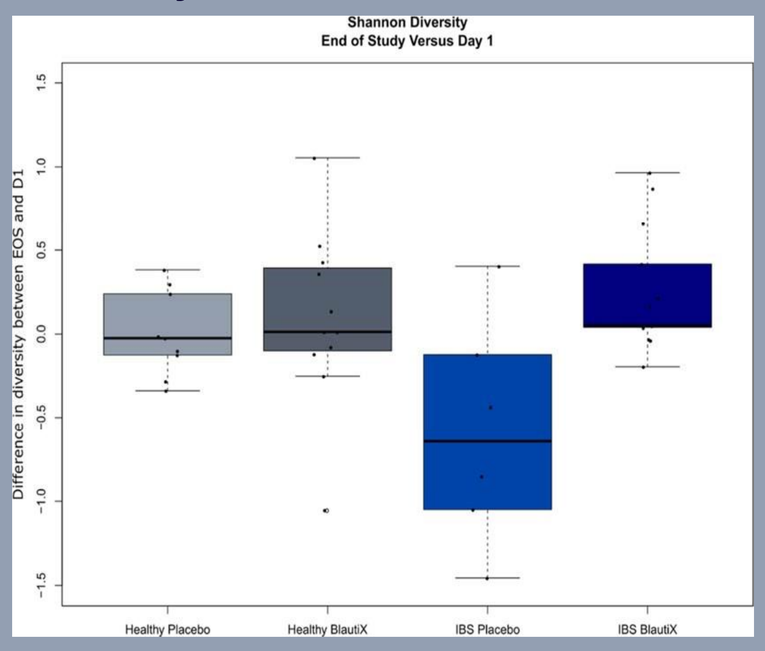
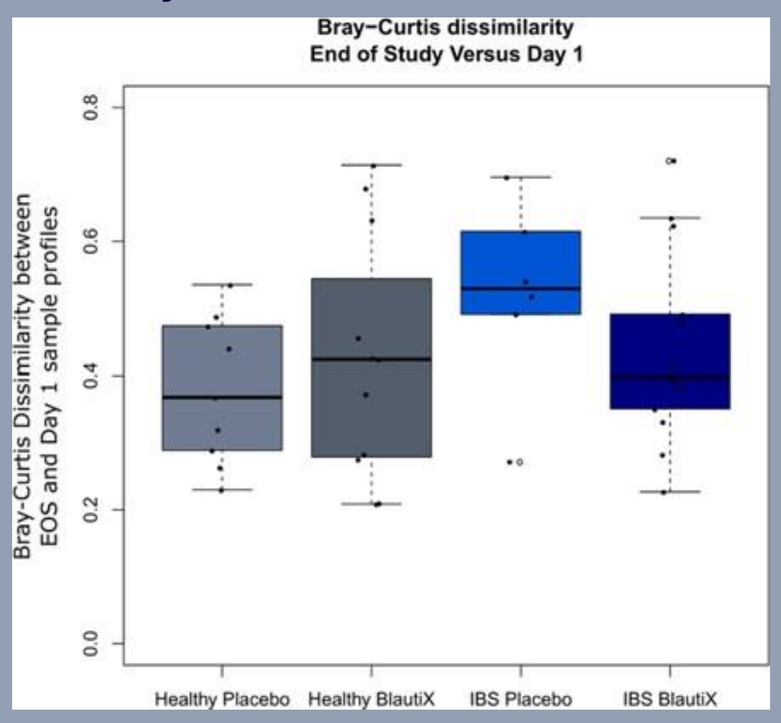


Figure 2. Effect on Abundance and Stability



Conclusions

- Treatment with BHT appears to increase the microbiota diversity and stability in patients with IBS.
- These effects appeared to be enduring for approximately 2 weeks after stopping treatment.
- BHT was well tolerated and some patients reported an improvement in IBS symptoms.
- Based on the findings that BHT positively impacts the gut microbiota, and the link between alterations in the microbiota and IBS, BHT represents a promising potential therapeutic option for patients with IBS.
- The treatment effects and impact on the gut microbiome of BHT should be explored in larger studies.