14 CLINICAL STUDIES

Clinical studies conducted to date have demonstrated the utility of dietary management with SBI in patients with some forms of enteropathy. Table 3 describes tolerance of SBI in healthy and diseased individuals as well as evidence that SBI manages symptoms of enteropathy in HIV infected patients and IBS-D subjects, lowers total and low-density lipoprotein (LDL) cholesterol in patients with mild hypercholesterolemia and improved nutritional status in infants and children.

Table 3. Impact of Dietary Management with SBI

Population Studied	**Impact of Dietary Management with SBI**
Healthy Adults N=12 (6 M; 6 F) Experiment 1: Double-blind, cross-over Single dose – SBI 10 g, Experiment 2: Open-label SBI – 2.5 g twice a day for 14 d	• In plasma, total amino acids at 90 and 120 minutes and leucine at 60 and 120 minutes were significantly higher ($p < 0.05$) following consumption of SBI 10 g. • Plasma amino acids returned to fasting levels by 90 minutes with control, but remained above baseline levels until 120 - 150 minutes after SBI 10 g. • No absorbed, intact IgG was detected in the plasma. • IgG activity present in stool on day 14. • Protein in SBI is digested in GI tract, resulting in higher plasma amino acid and leucine response 1-2 hrs after administration. Intact IgG activity is retained with passage through the GI tract.
HIV-associated Enteropathy Open-label pilot study, 8 HIV+ male adult patients, w/ HIV-associated enteropathy; median CD4+ cell count 372 cells/dL, SBI – 2.5 g twice a day for 48 weeks, (SBI for 8 weeks followed by 4 weeks washout and SBI for 48 weeks)	• Median bowel movements/day and stool consistency decreased at 8 weeks ($p = 0.013$). • Improvements in median GI symptoms questionnaire scores (cramping, urgency, incontinence, and nocturnal diarrhea at 8 weeks ($p = 0.013$). • Durable bowel movements/day, stool consistency and questionnaire responses were reported for those that continued SBI at week 48. • Marked improvement of GI-related symptoms within 3 weeks of initiating SBI in all 8 patients. • D-xylose absorption increased in 7/8 subjects, and in those with improvement, absorption levels increased from 31.4 mg to 41.5 mg ($p = 0.016$) at week 8. • Increased CD4+ T-lymphocyte density within lamina propria ($p = 0.0156$) after 8 weeks of SBI. • MCP-1 levels were unchanged at week 8 but decreased in 5/5 subjects at week 48 (379.5 ng/mL [225, 502]) ($p = 0.06$). • I-FABP initially rose in 7/8 subjects after 8 weeks from 3514 ng/mL to 4042 ng/mL ($p = 0.039$) and then fell below baseline in 4 of the 5 who continued receiving SBI to 2442 ng/mL at week 48 ($p = 0.12$). • MMP-9/TIMP-1 ratios in subjects were significantly lower than controls at baseline (0.13 versus 0.42 [$p = 0.007$]), respectively and tended to increase at the end of treatment to 0.33 ($p = 0.08$). • MCP-1 levels were negatively correlated to $CD3^+/CD4^+$ lamina propria density ($r = -0.59$, $p = 0.019$) with all time points examined. • MMP-9/TIMP-1 ratios were negatively correlated with $CD3^+/CD8^+$ lamina propria density ($r = -0.70$, $p = 0.0039$). • Baseline serum I-FABP levels were negatively correlated with subsequent rise in lamina propria $CD4^+$ T-lymphocytes ($r = -0.74$, $p = 0.046$). • Pro-inflammatory gammaproteobacteria tended to decrease and *Clostridium* (genus) tended to decrease. • Changes in gut microbiota correlated with local lymphocyte populations that increased significantly with 8 weeks of SBI therapy.

HIV-associated Enteropathy N=31, SBI 2.5 g-5.0 g/day	• A small in-market analysis of 31 patients taking various formulas with 2.5 g to 5.0 g SBI showed improved management of loose stools.
IBS-D Randomized, double-blind, placebo-controlled, single site, 6 week study N=66 patients diagnosed with IBS-D Placebo, SBI 5 g/day or SBI 10 g/day	• 10 g/d SBI group had a reduction in days with loose stools ($p = 0.011$), abdominal pain ($p = 0.008$), urgency ($p = 0.050$), bloating ($p = 0.044$); flatulence ($p = 0.003$); and any symptom ($p = 0.009$). • 5 g/day SBI group experienced reductions in days with flatulence ($p = 0.018$), incomplete evacuation ($p = 0.020$), and any symptom ($p = 0.010$).
Hypercholesterolemia Randomized, double-blind, placebo-controlled, 6 week study, N=52 patients w/ hypercholesterolemia Placebo or SBI 5.0 g	• SBI-treated group had a significant reduction in TC at 3 and 6 weeks ($p < 0.05$). • TC concentration at 6 weeks was significantly lower than placebo ($p < 0.05$). • TC reduction largely due to a decrease in LDL cholesterol in the SBI therapy group from baseline to 3 weeks ($p < 0.05$) and to 6 weeks ($p < 0.05$). • 6-week TC concentration differed significantly between the SBI and placebo groups ($p < 0.05$).
Malnutrition (Pediatric) Study 1: Randomized, controlled study N=10 (9-25 months) recovering from severe malnutrition Diet contained either control, or 25% or 50% milk protein replacement with SBI during 3 randomly ordered, 7 day dietary periods	Study 1 • The mean number of daily bowel movements, mean apparent absorption and retention of nitrogen, and mean apparent absorption of carbohydrate were similar for each diet. • Fractional absorption of dietary lipid and of total energy increased significantly in relation to the amount of SBI in the diet.
Study 2: Randomized, controlled, community based intervention study N=259 (6-7 months) Diet containing SBI, WPC, SBI + MMN or WPC + MMN daily for 8 months	Study 2 • No differences in growth or rates of morbidity by treatment group for those children who completed 8 months of observation. • Children receiving MMN had lower rates of anemia, and children who received WPC+MMN had less of a decline in serum ferritin. No differences in other biochemical indicators of micronutrient status were noted. • Supplementation with MMN reduced anemia and iron deficiency in this population, but the MMN content and source of protein in the supplements did not affect other indicators of micronutrient status, growth, or morbidity.

AE = adverse event; CD = cluster of differentiation antigen; GALT = gut associated lymphoid tissue; GI = gastrointestinal; IBS-D =irritable bowel syndrome-diarrhea predominant; HIV = human immunodeficiency virus; I-FABP = Intestinal fatty acid binding protein; LDL = low-density lipoproteins; LPS = lipopolysaccharide; MCP-1 = monocyte chemotactic protein-1; MMN = multiple micronutrients; MMP =

matrix metalloproteinase; SBI =serum-derived bovine immunoglobulin/protein isolate; sCD14 = soluble cluster of differentiation antigen 14; TC = total cholesterol; TIMP-1 = Tissue inhibitor of metalloproteinase 1; WPC = whey protein concentrate

SBI in ENTERAGAM has been self-affirmed as Generally Recognized as Safe (GRAS) with no objections from the FDA, a requirement for a medical food product. Table 4 presents a safety summary of current clinical studies.

Table 4. Safety Summary of Current Clinical Studies on SBI

Population Studied	**Safety Summary**
Healthy Adults	• 12 healthy adults ingested a single dose of 10 g SBI, followed by 2.5 g SBI twice a day for 14 days. SBI was generally well-tolerated by the subjects during the single bolus dose and over 14 days of ingestion. Reported AEs (subjects) included: increased urination (3), stomach cramps (3), fatigue (2), and headache (2), as well as sore throat, softened stools, nausea, constipation, and irritability (1 each).
HIV-associated Enteropathy	• Eight HIV+ adults ingested 2.5 g SBI twice a day for 8 weeks. SBI was well-tolerated and coincided with a reduction in HIV-associated enteropathy. Five patients continued on therapy for up to a year. The most commonly reported AEs included worsening or reoccurrence of diarrhea (5 AEs reported by 4 subjects), constipation (2 subjects), and worsening neuropathy (3 AEs reported by 2 subjects). AEs that were reported by 1 subject each included sinus infection, throat infection, gastroesophageal reflux disease, flatulence, worsening lower back pain, groin pain, nausea, bronchitis, acute ear infection, and infection on finger. None were reported to be related to SBI and no subjects discontinued due to an AE.
HIV-associated Enteropathy N=31 SBI 2.5 g-5.0 g/day	• A small in-market analysis of 31 patients taking various formulas with 2.5 g to 5.0 g SBI was performed. • SBI was well-tolerated and there were no significant AEs reported. No SAEs were reported.
IBS-D	• 34 adult subjects were treated for 6 weeks with either 5 or 10 g of SBI. This was well-tolerated with no SAEs reported. Three subjects withdrew from the study due to nausea. No statistically significant differences between groups with respect to hematology and clinical chemistry laboratory results.

Hypercholesterolemia	• 52 adult subjects ingested 5g SBI or placebo for 6 weeks. No significant changes in lipid indices or markers associated with hepatorenal or cardiovascular function were observed.
Malnutrition (Pediatric)	10 children (9-25 months) were provided a diet with either 25 or 50% protein replacement of milk protein with SBI during 3 randomly ordered, 7 day dietary periods. There were no reported AEs due to SBI.
	• 107 (6-7 months) infant children received SBI in the 8 month study. There were no reported AEs due to SBI.

AE=adverse event; HIV=human immunodeficiency virus; IBS-D=irritable bowel syndrome-diarrhea predominant; SAEs = Serious adverse events; SBI=serum-derived bovine immunoglobulin/protein isolate