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FOOD STUDY PROTOCOL

Clinical Study Number: WB01-202_Version 2 Amendment 3

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Date:

Study Name: An Exploratory Placebo-Controlled Study to Evaluate the Safety and Metabolic Effects of Food Products WBF-0010 and WBF-0011 When Administered to Subjects with Type 2 Diabetes Treated with Diet and Exercise Alone or in Combination with Metformin and/or Sulfonylurea

Type of Study: Food Research Discovery

Investigator: Orville G. Kolterman, MD

Study Site: Up to 6 clinical sites (to be named) within the United States.

Sponsor(s): Whole Biome, Inc., 933 20th Street, San Francisco, CA 94107

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Abbreviations List:

- (Hemoglobin) A1c: glycated hemoglobin
- ADL: activities of daily living
- AEs: adverse events
- ALT: alanine aminotransferase
- AST: aspartate aminotransferase
- BMI: body mass index
- CFU: colony forming units
- CI: confidence intervals
- CPK: creatine phosphokinase
- CRF: case report form
- CRP: c-reactive protein
- ECG: electrocardiogram
- GCP: good clinical practice
- GGT: gamma glutamyltranspeptidase
- GLP-1: glucagon-like peptide-1
- GMP: good manufacturing practice
- GPR41: G protein-coupled receptor 41
- GPR43: G protein-coupled receptor 43
- GRAS: generally recognized as safe
- HADS: Hospital Anxiety and Depression Scale
- HDL cholesterol: high-density lipoprotein cholesterol
- HIPAA: Health Insurance Portability and Accountability Act
- HOMA-IR: homeostatic model assessment for insulin resistance
 - (<https://www.dtu.ox.ac.uk/homacalculator/>)
- ICF: informed consent form
- IL-10: interleukin 10
- IL-6: interleukin 6
- IRB: institutional review board
- ITT: intent-to-treat
- LDL cholesterol: low-density lipoprotein cholesterol
- Matsuda Index:
 - Formula: $ISI(comp) = 10,000 / \sqrt{[(G_0 \times I_0)(G_{mean} \times I_{mean})]}$
 - G_0 – Fasting plasma glucose concentration (mg/dl)
 - I_0 – Fasting plasma insulin concentration (mIU/l)
 - G_{mean} – Mean plasma glucose concentration during OGTT (mg/dl)
 - OGTT – oral glucose tolerance test
 - I_{mean} – Mean plasma insulin concentration during OGTT (mU/l)

- 10,000– Simplifying constant to get numbers from 0 to 12
- $\sqrt{}$ – Correction of the nonlinear values distribution
- MedDRA: medical dictionary for regulatory activities
- MTT: meal tolerance test
- NCI-CTCAE: National Cancer Institute- Common Terminology Criteria for Adverse Events
- SAE: serious adverse event
- SAP: statistical analysis plan
- SCD: stool collection device
- SCFA: short chain fatty acid
- SCK: stool collection kit
- TEAEs: treatment emergent adverse events
- TGF- β : transforming growth factor beta
- TGs: triglycerides
- TNF- α : tumor necrosis factor alpha
- U/A: urine analysis
- $\Delta\text{AUC}_{\text{glucose (0-180)}}$: area under the glucose curve from T=0-180 minutes
- $\Delta\text{AUC}_{\text{insulin}}$: area under the insulin curve

A. Background:

Diabetes mellitus and its comorbidities are currently a global, public health crisis, with approximately 30 million people diagnosed with diabetes and an estimated 80 million additional people with prediabetes in the US alone. Although diabetes is a multifactorial disease, it is widely believed that the proliferation of diabetes worldwide can be largely attributed to the adoption of the Western diet. Recently, research has shown that the use of the Western diet has significant impacts on the gut microbiome, altering both the composition and activities of that microbiome (The microbiome refers to the bacteria, viruses, fungi, phage, and other microorganisms that reside in the human intestine).

An individual's gut microbiome contains 10 to 100-fold more genetic information than resides in the host's genome. There is increasing evidence that the gut microbiome offers an opportunity for the development of novel interventions for a variety of diseases by modulating the composition of the gut microbiome. Specific bacterial strains in the gut microbiome ferment indigestible dietary fibers in the colon to produce short chain fatty acids (SCFAs), such as acetate, propionate, and butyrate (Nohr-2013). Use of the Western diet leads to a reduction in both the number and density of butyrate-producing microbes. SCFAs, and butyrate in particular, bind to multiple G protein-coupled receptors, GPR41, GPR43, and GPR119, which trigger the downstream signaling pathway for GLP-1, a hormone known to play a key role in the development and progression of diabetes. These observations have led to a hypothesis that replenishing the content of butyrate microbes in the intestinal tracts of these individuals will have beneficial metabolic effects.

In addition to these metabolic effects, increasing butyrate production within the colon in individuals with the metabolic syndrome, including type 2 diabetes, may improve the integrity of mucin layer which lies atop the colonic mucosa and serves as a barrier against the entry of bacteria and bacterial fragments into the bloodstream. This stems from the demonstration that butyrate is an important energy source for colonic mucosal cells. This "butyrate effect", coupled with increased barrier regulation by other bacterial strains, is expected to contribute to the integrity of the colonic mucin layer. This mucin layer functions to reduce the influx of bacterial antigens, which are postulated to foster the general inflammatory state associated with the metabolic syndrome.

Whole Biome has developed a proprietary discovery platform which utilizes high resolution throughput DNA sequencing with the capability to identify individual bacterial strains. Whole Biome has applied this platform to identify potentially beneficial strains, e.g., specific butyrate-producing microbial strains that are less abundant or missing in patients with type 2 diabetes. With this knowledge, Whole Biome is developing a medical food containing a subset of commensal butyrate-producing strains that can be grown under controlled conditions that meet the standards for Good Manufacturing Practice (GMP), thus allowing administration to humans. In addition, barrier permeability-regulating strains have also been identified and produced in a similar manner for use in human studies.

B. Purpose:

The overall goal of this study is to test the hypothesis that oral supplementation with a medical food designed to increase butyrate production and promote the health of the colonic mucin layer will improve metabolic health. The medical food formulations being tested in this study contain butyrate-producing organisms with or without a barrier permeability-regulating strain.

Patients with type 2 diabetes exhibit both deranged carbohydrate metabolism and a generalized inflammatory state. Inflammation in skeletal muscle, adipose tissue, and the liver contribute to insulin resistance, which in conjunction with decreased insulin secretion, account for the abnormalities in carbohydrate metabolism. Recent studies indicate that these metabolic and inflammatory changes are accompanied by the depletion of butyrate-producing and barrier permeability-regulating organisms within the gut microbiome.

In this exploratory intervention study, we intend to evaluate these issues within patients with early stage type 2 diabetes. This includes patients diagnosed but not exposed to anti-diabetic therapy and patients treated with the most commonly used initial treatment regimen, i.e. metformin and/or sulfonylurea. Two different medical food formulations will be tested: a formulation containing 2 butyrate-producing microbes and a third formulation consisting of the first formulation with approximately matching colony forming units (CFUs) of a third butyrate producer plus a barrier permeability-regulating strain, which has been associated with improved gut-epithelial barrier function in rodent studies. Subjects will receive their randomized formulation twice a day for 12 weeks, followed by a 4-week washout period.

C. Study Product Safety:

All bacteria contained in the study product formulations used in this study are commensal organisms that have been repeatedly documented to inhabit the human GI tract under normal circumstances. The organisms were grown under controlled conditions consistent with Good Manufacturing Practices (GMP) and employ no animal-derived products. All ingredients utilized during manufacturing were food grade and qualified as generally recognized as safe (GRAS). Each of the microbes have been characterized in detail (including whole genome sequencing) to ensure that mutations have not occurred. Each manufactured lot has also been tested with standard methods to ensure the absence of toxins, heavy metals, etc.

All strains have also been tested *in vivo* in both a diet-induced obese mouse model and Sprague-Dawley rats. Each of these rodent models were dosed for 28 days at multiples ≥ 60 times (based on body weight) the amounts being administered in this study. In each study, safety was evaluated by clinical observation, routine chemistry, and hematology parameters, in addition to necropsy evaluation at study conclusion. In both studies no clinical, laboratory, or necropsy observations were observed that suggest adverse effects. In addition, a 5-person safety study was conducted with administration of 3 of the strains for 14 days using portions that were in excess of those proposed here without observing any adverse events or tolerability issues (See Portion Size

Selection). For the other 2 strains, WB-STR-0001 and WB-STR-0008, this study will be the first exposure to humans.

D. Study Design:

This is a balanced, parallel-arm, double-blind, placebo-controlled study with the following 3-treatment arms:

1. Placebo (WBF-0009: excipients only)
2. WBF-0010 (two butyrate-producing strains)
3. WBF-0011 (WBF-0010 + an additional butyrate-producing strain + a barrier permeability-regulating strain)

The study is designed to test the hypothesis that oral administration of encapsulated formulations of the study products is safe and well-tolerated and yields beneficial metabolic and/or anti-inflammatory effects following administration for 12 weeks.

Primary Endpoint:

The primary endpoints for this exploratory study is the assessment of safety and tolerability, as assessed by adverse events; the efficacy endpoint is the change from baseline to Week 12 in the area under the glucose curve ($\Delta\text{AUC}_{\text{glucose (0-180)}}$) during a standardized 3-hour meal tolerance test (MTT); and the primary inflammatory endpoint is the change from baseline to Week 12 in c-reactive protein (CRP).

Secondary Endpoints:

1. Assessment of change in the area under the insulin curve ($\Delta\text{AUC}_{\text{insulin}}$) from baseline to Week 12 during standardized meal tolerance test
2. Assessment of change in fasting glucose from baseline to Weeks 4, 12, and 16
3. Assessment of change in fasting insulin from baseline to Weeks 4, 12, and 16
4. Change in hemoglobin A1c from baseline to Weeks 4 and 12
5. Change in inflammatory markers from baseline to Weeks 4 and 12:
 - a. C-reactive protein (CRP)
 - b. IL-6
 - c. TNF- α
6. Change in additional inflammatory markers from baseline to Week 12:
 - a. IL-10
 - b. TGF- β
7. Assessment of change in homeostatic model assessment for insulin resistance (HOMA-IR) from baseline to Week 12

(<https://www.dtu.ox.ac.uk/homacalculator/>)

8. Assessment of change in the Matsuda index from baseline to Week 12 [Formula for Matsuda index: $ISI(\text{comp}) = 10,000 / \sqrt{[(G_0 \times I_0)(G_{\text{mean}} \times I_{\text{mean}})]}$, where
 - G_0 – Fasting plasma glucose concentration (mg/dl)
 - I_0 – Fasting plasma insulin concentration (mIU/l)
 - G_{mean} – Mean plasma glucose concentration during OGTT (mg/dl)
 - OGTT – oral glucose tolerance test
 - I_{mean} – Mean plasma insulin concentration during OGTT (mIU/l)
 - 10,000– Simplifying constant to get numbers from 0 to 12
 - $\sqrt{}$ – Correction of the nonlinear values distribution
9. Assessment of change in fasting lipid panel [total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides (TGs)] from baseline to Weeks 4, 12, and 16
10. Change in body weight from baseline to Weeks 2, 4, 12, and 16
11. Change in BMI from baseline to Weeks 2, 4, 12, and 16
12. Change in waist circumference between baseline and Week 12
13. Change in fecal microbiome from baseline to Weeks 4, 12, and 16
14. Change in responses to Hospital Anxiety and Depression Scale (HADS) questionnaire from baseline to Week 12
15. Change in response to FACIT D&AD and Victoria Bowel Performance Scale Questionnaire

Following completion of the Week 12 visit, subjects will discontinue study product. They will then return to the clinic for a final visit at the end of Week 16, bringing with them a frozen stool sample collected during the prior 3 days to assess the persistence of the administered microorganisms in stool ~4 weeks after discontinuing ingestion. In addition, fasting glucose, insulin, and lipid panel will be collected at Week 16 to evaluate the persistence of changes in these parameters.

E. Study Product Portion Selection:

Selection of study product portion size was guided by the exposure in Sprague-Dawley rats for 28 days and a human safety study as described above under Study Product Safety. In the human safety study, subjects consumed 7.0×10^9 CFU of strain WB-STR-0005, 4.0×10^9 CFU of strain WB-STR-0006, and 2.0×10^8 CFU of strain EXT-STR-0001 daily for 7 days, followed by a 5-fold increase in consumption to 3.5×10^{10} CFU of strain WB-STR-0005, 2.0×10^{10} CFU of strain WB-STR-0006, and 1.0×10^9 CFU of strain EXT-STR-0001 daily for an additional 7 days. The administered strains were detected in stool by the end of the first week of consumption, with an

increase in quantity following the 5-fold increase in consumption.

F. Study Structure:

This is a balanced, parallel-arm, double-blind, placebo-controlled study consisting of an initial screening visit, a randomization visit on Day 0, and subsequent visits at Weeks 2, 4, 8, 12, and 16. In addition, phone visits will be conducted at Weeks 6 and 10 to ensure timely capture of adverse events and promote compliance.

Table 1: Daily Microbial Ingestion in Study Product

Intervention	WB-STR-0006 (CFU/day)	WB-STR-0005 (CFU/day)	EXT-STR-0001 (CFU/day)	WB-STR-0001 (CFU/day)	WB-STR-0008 (CFU/day)
Placebo (WBF-0009)	Colloidal silicon dioxide, a non-active GRAS ingredient.				
WBF-0010	3.3×10^9	1.6×10^{10}	2.0×10^9	None	None
WBF-0011	3.3×10^9	1.6×10^{10}	2.0×10^9	1.2×10^9	9.0×10^8

The screening visit to qualify for participation will happen between Day -7 and Day -14. Randomization will happen at the Day 0/Baseline visit along with the initiation of the randomly assigned study product twice daily, 3 capsules taken within 30 minutes before each morning and evening meal. Administration of study product will cease at the time of the 12-week visit as the subjects enter a 4-week wash-out period. At the final visit at the end of Week 16, the subjects will be asked to bring 1 frozen stool sample collected during the preceding 3 days to assess the persistence of the administered organisms in stool. Monitoring for adverse effects will also continue through Week 16 and any Week 12 lab abnormalities in safety lab tests will be followed up.

A medical history review will be done at screening with interim history reviews at Week 12 and Week 16. A physical examination will be performed at baseline and Week 12. Stool samples will be collected at baseline, Week 4, Week 12, and Week 16. In addition, phone visits will be conducted at Weeks 6 and 10 to collect unsolicited, spontaneous adverse events, review concomitant medications, and assess compliance with study product.

The Hospital Anxiety and Depression Scale (HADS) is integrated as part of the EDC system and will be completed at baseline (Visit 1) and week 12 (Visit 7). The FACIT D&AD and Victoria Bowel Performance Scale (BPS) will be optional and completed twice; at week 12 (Visit 7) and again at week 16 (Visit 8). Sites will scan and email or fax the completed optional questionnaires to the sponsor for data entry.

Figure 1: Overview of Study Design

<u>Screening Visit: -7 to -14 days</u> <ul style="list-style-type: none"> • Consents • Inclusion/Exclusion • Weight, Vital Signs, BMI, Height • History • Screening Labs • Con Meds + AEs • Dispense SCK 	<u>Visit 2: Week 2</u> <ul style="list-style-type: none"> • Weight, Vital Signs, BMI • Con Meds + AEs • Study Product Compliance • Dispense Study Product • Dispense SCK 	<u>Visit 5: Week 8</u> <ul style="list-style-type: none"> • Con Meds + AEs • Study Product Compliance • Dispense Study Product • Dispense SCK 	<u>Visit 8: Week 16</u> <ul style="list-style-type: none"> • Collect SCK • Fasting Plasma Glucose • Fasting Insulin • Fasting Lipid Panel • Medical History (Interim) • Weight, Vital Signs, BMI • Con Meds + AEs • Questionnaires
<u>Visit 1: Day 0</u> <ul style="list-style-type: none"> • Collect SCK • Randomization • MTT • Hemoglobin A1c • Fasting Lipid Panel • Questionnaires • Safety Labs + U/A + Inflammatory Markers • Weight, Vital Signs, BMI, Waist Circumference • Physical Exam • ECG • Con Meds + AEs • Dispense Study Product 	<u>Visit 3: Week 4</u> <ul style="list-style-type: none"> • Collect SCK • Hemoglobin A1c • Fasting Plasma Glucose • Fasting Insulin • Fasting Lipid Panel • Safety Labs + Inflammatory Markers • Weight, Vital Signs, BMI • Con Meds + AEs • Study Product Compliance • Dispense Study Product 	<u>Visit 6: Week 10 (Phone Visit)</u>	<p><u>NOTE: Phone Visits (Weeks 6 and 10):</u></p> <ul style="list-style-type: none"> • Con Meds + AEs • Study Product Compliance
	<u>Visit 4: Week 6 (Phone Visit)</u>	<u>Visit 7: Week 12</u> <ul style="list-style-type: none"> • Collect SCK • MTT • Hemoglobin A1c • Fasting Lipid Panel • Questionnaires • Safety Labs + U/A + Inflammatory Markers • Medical History (Interim) • Weight, Vital Signs, BMI, Waist Circumference • Physical Exam • ECG • Con Meds + AEs • Dispense SCK 	

Abbreviations: SCK = "Stool Collection Kit"

Note: "Fasting Lipid Panel" includes fasting total cholesterol, TGs, LDL cholesterol, and HDL cholesterol; "Inflammatory Markers" include CRP, IL-6, IL-10, TNF- α , and TGF- β at Visit 1 (Day 0) and Visit 7 (Week 12); at Visit 3 (Week 4), only CRP, IL-6, and TNF- α are collected.

G. Duration:

The total duration of a subject's participation will be approximately 18 weeks, including the screening visit occurring 7 to 14 days prior to the baseline visit at Day 0. At the baseline visit, collection of baseline measures, randomization, and initiation of study product consumption will occur. Following the initiation of study product, active participation will extend through Week 16 (See **Appendix 1** for a display of study procedures by study visit).

H. Number of Subjects:

It is anticipated that approximately 90 subjects will be screened with ~75 subjects randomized to yield ~60 subjects completing the study (~20 subjects/arm). All subjects will have been diagnosed with type 2 diabetes and currently treated with diet and exercise alone or in combination with metformin and/or sulfonylurea.

I. Inclusion Criteria:

1. Age: 18 to 75 years of age
2. Have type 2 diabetes treated with diet and exercise alone or in combination with metformin and/or sulfonylurea
3. If treated with metformin and/or sulfonylurea, must have been on a stable dose of the drug(s) for a minimum of 3 months with a stable A1c value
4. If treated with diet and exercise alone, must have one of the following:
 - a. Documented fasting plasma glucose >126 mg/dL
 - b. A1c value \geq 6.8%
5. If treated with diet and exercise + metformin and/or sulfonylurea, must have a stable A1c between 6.8% and 11.0% for approximately 3 months
6. BMI >25 but <45 and weight stable within +/- 5% over past 3 months
7. If female, must meet all the following criteria:
 - a. Not pregnant or breastfeeding
 - b. If of childbearing potential (including peri-menopausal women who have had a menstrual period within one year) must practice and be willing to continue to practice appropriate birth control (defined as a method which results in a low failure rate, i.e., less than 1% per year, when used consistently and correctly, such as double barrier methods [male condom with spermicide, with or without cervical cap or diaphragm], implants, injectable or oral contraceptives [must have been using for at least the last 3 months], some intrauterine contraceptive devices, tubal ligation, or in an established relationship with a vasectomized partner) during the entire duration of the study
8. Have a home freezer available for immediate freezing of stool samples
9. Able to read, understand, and sign the informed consent form (ICF) and, when applicable, an authorization to use and disclose protected health information form (consistent with Health Insurance Portability and Accountability Act of 1996 [HIPAA] legislation as modified in 2013)
10. Able to communicate with the investigator, and understand and comply with protocol requirements

J. Exclusion Criteria:

1. Subjects who have received an antibiotic, antifungal, antiparasitic, or antiviral treatment within 30 days prior to study entry
2. Subjects who plan to use antibiotic, antifungal, antiparasitic, or antiviral treatment during the study
3. Subjects using a proton pump inhibitor must be on a stable dose that will be maintained throughout the study period
4. Present use of probiotics/nutritional supplements. (Note: The use of replacement doses of Vitamin D, calcium supplements, and a single daily multi-vitamin tablet is allowed)
5. Subjects who have participated in a structured weight-loss program within the past 2 months
6. Subjects who have changed body weight $\geq 5\%$ within the past month
7. Excess alcohol consumption; with an alcoholic drink defined as 12 fluid ounces of beer (5% alcohol), 5 fluid ounces of wine (12% alcohol) or 1.5 fluid ounces of 80 proof distilled spirits
 - a. Women: More than 2 alcoholic drinks/day or more than 7 drinks/week
 - b. Men: More than 3 alcoholic drinks/day or more than 10 drinks/week
8. Subjects who have travelled outside the United States within 30 days prior to study entry
9. Subjects who plan to travel outside the United States during the projected study period
10. Subjects who have received an experimental drug within 30 days prior to study entry
11. Subjects with known milk, peanut, tree nut, wheat, soy or shellfish allergies
12. Subjects who have been diagnosed with a sexually transmitted disease including, but not limited to, HIV, syphilis, herpes, gonorrhea, hepatitis A, hepatitis B, and hepatitis C
13. Hospitalization for any reason within the 3 months prior to study entry (Same day surgery center visits/procedures allowed)
14. Any active GI disease
15. History of any surgery on the gastrointestinal tract except appendectomy and cholecystectomy
16. Cystic fibrosis
17. Subjects with any condition that the investigator deems as a sound reason for disqualification from enrollment into the study

K. Removal of Subjects from Study Participation:

1. Withdrawal of Consent - Subject wishes to withdraw from the study as outlined in the informed consent form. All subjects reserve the right to withdraw from the study without prejudice to themselves or their future medical care.
2. Adverse Event - Subject experiences an adverse event, which in the investigator's opinion necessitates withdrawal from the study.
3. Investigator Decision - Investigator assessment that it is in the subject's best interest to terminate participation.
4. Protocol Violation – Includes subject non-compliance, documented pregnancy, study entry criteria violation, and/or initiation of an unacceptable concomitant medication, especially antibiotics, unless approved by Sponsor.
5. Lost to Follow-Up - Subject fails to return for study visits and cannot be reached with reasonable attempts.
6. Administrative Reason – Includes discontinuation of the study protocol by the sponsor, the Food and Drug Administration (FDA), or other regulatory authority, and/or discontinuation of the study site's participation in the study protocol.

Any withdrawal from the study will be fully documented. The documentation will include reasons for the withdrawal and details of any sequelae (followed through until the symptoms have resolved or returned to baseline levels) if the reason for withdrawal was an adverse event. Whenever possible, subjects terminating early will have the procedures outlined in Visit 7. **(Note: If the subject has been receiving Study Product for <4 weeks, the MTT and inflammatory markers should be omitted.)**

L. Subject Information and Samples:

Once screened and qualified for entry, subjects will be instructed as follows:

1. Take no new prescription or over-the-counter medications excluded by the protocol without prior notification of the investigator.
2. Remain on their usual diet and exercise regimen throughout the study unless instructed to change by the investigator.
3. Fast overnight for at least 8 hours (no food or beverage except water) prior to each study visit except for the Screening Visit. (Note: This includes tea and coffee.)
4. Not donate blood for the duration of the study.

The sponsor should be contacted if the investigator is informed of any violations of these restrictions. The sponsor will decide whether a subject with restriction violations will be granted

a deviation and allowed to continue study participation.

M. Study Food Product:

Study product will consist of coated capsules designed to pass through the stomach intact and disintegrate in the terminal portion of the small intestine. Subjects will be instructed to take 3 capsules of the food product within 30 minutes before each morning and evening meal, beginning with the evening meal on the day of randomization (Visit 1, Day 0) through the completion of Visit 7 (Week 12). The capsules will be identical in general appearance, size, and color across all the treatment arms. Each medical food study formulation capsule will contain the designated butyrate and barrier permeability-regulating commensal strains (Table 1); and consistent amounts of inulin, sucrose, trehalose, glycerin, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, titanium dioxide, polyvinylpyrrolidone, skim milk, and colloidal silicon dioxide. Placebo (WBF-0009) capsules will contain colloidal silicon dioxide. Commensal microbes are grown under GMP conditions using GRAS certified food grade reagents. All other ingredients are GRAS certified.

1. Packaging and Storage

The study food product will be provided in sealed, labelled screw cap bottles. Each bottle will contain 45 capsules to support 7 days of administration (42 capsules), plus 3 excess capsules to allow for replacement of lost capsules, etc. Additionally, the capsules for all treatment arms, including placebo (WBF-0009), will be identical in appearance to support the study blind.

The study food product should be refrigerated at 2-8 °C except when the subject removes the bottle to take out 3 capsules scheduled for ingestion within 30 minutes before the upcoming morning or evening meal. Once 3 capsules have been removed, the bottle should be tightly capped and returned to the refrigerator immediately.

2. Dispensing of Study Food Product

Study materials will be provided to subjects by the investigator, sub-investigator, or other medically qualified study-site personnel. Under no circumstance will the investigator or sub-investigator(s) allow the study product to be used other than as directed by the protocol or to be administered to any persons other than subjects who have signed an informed consent form and are participating in the study.

Study-site personnel will be responsible for instructing subjects to administer the correct amounts of study product, i.e. 3 capsules before each morning and evening meal. Again, the capsules should be taken within 30 minutes before the start of the morning and evening meals.

3. Study Product Accountability

The investigator listed on form FDA 1572 will be responsible for study accountability. Upon receipt of all study product at the clinical study site, the contents of each shipment

will be verified against the enclosed shipping form and the bar codes on the individual bottles scanned into the electronic data management system. After verification of the accuracy of the shipment, the form will be signed and dated, a copy retained for the investigator's file, and the original returned to the sponsor. The sponsor will be notified immediately if any irregularities, discrepancies, or damages are identified.

Following verification of the shipment, the study product should be maintained in a refrigerated environment within a secure, locked refrigerator or in a secured area at the study site with access restricted to authorized personnel. The refrigerator used for study product storage should be monitored for temperature control with the monitoring results logged. The bottles of investigational materials will be dispensed only by the investigator, sub-investigators, or designated study personnel at the time of study site visits. **Under no circumstances will the investigator or sub-investigators allow the study product to be used other than as specified in the protocol.**

4. Amount Administration, Route and Schedule

Three (3) capsules of study food product will be orally self-administered by the subject within 30 minutes prior to each morning and evening meal, as described above.

Study product dispositions and returns will be recorded on a sponsor-provided study product disposition form, to provide a complete accounting of the receipt, disposition, and return of each bottle of study product. As empty study product bottles are returned throughout the study, the bottles should be disposed of in an appropriate manner once the compliance assessment has been completed. At completion of Visit 7, the remaining unused study product will be returned to the sponsor or their designee.

Note: Due to packaging constraints (1 week supply with 3 extra capsules/bottle), the extra capsules should be utilized whenever possible to cover additional dosing to allow visit windows of -2 days to +2 days (+2 days only on Visit 7/week 12). Thus, subjects should be instructed to use all available capsules before opening a new bottle of study product. By capturing and utilizing these extra capsules, the visit windows for the study will be as follows (calculations based on defining the Baseline Visit as Day 0) : Visit 2 (Day 12 to Day 15), Visit 3 (Day 26 to Day 30), Visit 4 (Day 38 to Day 42), Visit 5 (Day 54 to 58), Visit 6 (Week Day 68 to Day 72), Visit 7 (Day 82 to 86) and Visit 8 (Day 110 to Day 114)

N. Study Visits:

Prior to all study visits (screening visit excluded), subjects will be asked to fast overnight for at least 8 hours (i.e., no food or beverage except water). Subjects should report to the clinical study site in the morning of each scheduled visit (ideally between 0800 and 0900 hours). For all study visits, which require the subjects to be fasting, the subjects should refrain from administering the morning portion of study product prior to the visit, and bring the morning's

portion of study product with them to the study-site to take in conjunction with their morning meal after the fasting blood work has been completed.

1. Screening Visit (Day-14 to Day -7)

The following items will be addressed during the Screening Visit:

- a. The informed consent and HIPAA authorization forms will be signed prior to performing any study procedures
- b. Review of inclusion/exclusion criteria to evaluate and confirm subject eligibility
- c. Complete medical history
- d. Collect vital signs, height, weight, and BMI
- e. Review of concomitant medications
- f. Blood sample collection for the following assessments:
 - i. HIV, Hepatitis C, Hepatitis B, Hepatitis A serologies
 - ii. Serum pregnancy test
 - iii. Chemistry panel (includes glucose, urea nitrogen, creatinine, total protein, albumin, uric acid, total and fractionated bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyltranspeptidase (GGT), creatine phosphokinase (CPK), sodium, potassium, chloride, bicarbonate, phosphate, calcium, and magnesium)
 - iv. Hematology panel (includes red cell count, hemoglobin, hematocrit, white cell count, platelets, differential count, mean cell volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration)
 - v. Hemoglobin A1c
- g. Review instructions for stool collection [Appendix 2] and dispense a stool collection kit for collection of a stool sample prior to the baseline visit (Visit 1/Day 0). (Note: Subjects should be instructed to freeze the sample in their home freezer immediately after collection and bring the sample frozen to the clinic at their next visit)

2. Baseline (Visit 1/Day 0)

The following procedures will be completed at Visit 1:

- a. Physical examination, including vital signs, weight, BMI, and waist circumference

- b. Review of concomitant medications
- c. Adverse event review
- d. Delivery of the baseline frozen stool sample to clinic staff
- e. Establish venous access for conduct of the standardized Meal Tolerance Test (MTT) according to the procedures outlined in **Appendix 3** (Blood samples for the measurement of plasma glucose and insulin at T=0, 30, 60, 90, 120, and 180 minutes relative to ingestion of a standardized liquid mixed meal (Boost Plus™, 475 mL = 720 calories)
- f. Using the established venous access, draw bloods for the following **prior to ingestion of the meal:**
 - (i) Chemistry and hematology panels (Safety labs)
 - (ii) Hemoglobin A1c
 - (iii) Fasting total cholesterol, TGs, LDL, and HDL cholesterol (unless included in chemistry panel)
 - (iv) Inflammatory marker panel (CRP, IL-6, IL-10, TNF- α , and TGF- β)
 - (v) 10 mL of blood for a frozen, stored serum sample for the measurement of other hormones, short chain fatty acids, and other metabolites, should study results warrant
- g. ECG
- h. Urine Analysis
- i. Complete Hospital Anxiety and Depression Scale [**Appendix 4**] questionnaire
- j. Dispense 2-week supply of study food product (Bottles 1 and 2) Open the initial bottle of study product and review instructions with the subject for taking study food product within 30 minutes before each morning and evening meal. The subject should take the initial 3 capsules of study product with some food prior to leaving the study site.
- k. Subjects should be instructed to only bring empty bottles with them to clinic for future visits, i.e. leave the bottle currently in use in their refrigerator at home. Since subjects need to come to clinic fasting, they should be instructed to bring 3 capsules with them for ingestion with a snack once their fasting blood samples have been drawn.

3. Visit 2 (Week 2)

The following procedures will be completed at Visit 2:

- a. Collect vital signs, weight, and BMI
- b. Review concomitant medications
- c. Non-directed review of adverse events
- d. Review study product use, assess compliance, and address any barriers to study product use
- e. Dispense 2-week supply of study food product (Bottles 3 and 4)
- f. Dispense a stool collection kit for collection of a stool sample within the 3 days prior to Visit 3 (Week 4). (Note: Subjects should be instructed to freeze the sample in their home freezer immediately after collection and bring the sample frozen to the clinic at their next visit)

4. Visit 3 (Week 4)

The following procedures will be completed at Visit 3:

- a. Collect vital signs, weight, and BMI
- b. Review concomitant medications
- c. Non-directed review of adverse events
- d. Review study product use, assess compliance, and address any remaining barriers to study product use
- e. Delivery of the frozen stool sample collected during the prior 3 days to clinic staff
- f. Blood sample collection (**fasting samples**) for the following assessments:
 - (i) Fasting insulin
 - (ii) Chemistry and hematology panels (Safety labs)
 - (iii) Hemoglobin A1c
 - (iv) Fasting total cholesterol, TGs, LDL, and HDL cholesterol (unless included in chemistry panel)
 - (v) Inflammatory marker panel (CRP, IL-6, and TNF- α)
- g. Dispense 1-month supply of study food product (Bottles 5-8)

5. Visit 4 (Week 6, Phone Visit)

The following procedures will be completed at Visit 4:

- a. Review of concomitant medications

- b. Non-directed review of adverse events
- c. Review study product use, assess compliance, and address any remaining barriers to study product use

6. Visit 5 (Week 8)

The following procedures will be completed at Visit 5:

- a. Review of concomitant medications
- b. Non-directed review of adverse events
- c. Review study product use, assess compliance, and address any remaining barriers to study product use
- d. Dispense 1-month supply of study food product (Bottles 9-12)
- e. Dispense a stool collection kit for collection of a stool sample within the 3 days prior to the Week 12 visit. (Note: Subjects should be instructed to freeze the sample in their home freezer immediately after collection and bring the sample frozen to the clinic at their next visit)

7. Visit 6 (Week 10, Phone Visit)

The following procedures will be completed at Visit 6:

- a. Review of concomitant medications
- b. Non-directed review of adverse events
- c. Review study product use, assess compliance, and address any remaining barriers to study product use
- d. Remind subjects to collect a stool sample during the 3 days prior to next visit, freeze the sample in their home freezer immediately after collection, and bring the sample frozen to the clinic at their next visit

8. Visit 7 (Week 12)

The following procedures will be completed at Visit 7:

- a. Review of interim medical history
- b. Physical examination, including vital signs, weight, BMI, and waist circumference
- c. Review of concomitant medications
- d. Non-directed review of adverse events
- e. Delivery of the frozen stool sample collected during the prior 3 days to clinic staff
- f. Establish venous access for conduct of the standardized Meal Tolerance

Test (MTT) according to the procedures outlined in **Appendix 3** (Blood samples for the measurement of plasma glucose and insulin at T=0, 30, 60, 90, 120 and 180 minutes relative to ingestion of a standardized liquid mixed meal (Boost Plus™, 475 mL = 720 calories)

- g. Using the established venous access, draw bloods for the following tests **prior to ingestion of the meal:**
 - (i) Chemistry and hematology panels (Safety labs)
 - (ii) Hemoglobin A1c
 - (iii) Fasting total cholesterol, TGs, LDL, and HDL cholesterol (unless included in chemistry panel)
 - (iv) Inflammatory marker panel (CRP, IL-6, IL-10, TNF- α , and TGF- β)
 - (v) 10 mL of blood for a frozen, stored serum sample for the measurement of other hormones, short chain fatty acids, and other metabolites, should study results warrant
- h. Complete Hospital Anxiety and Depression Scale [**Appendix 4**] questionnaire
- i. Complete **optional** FACIT D&AD Questionnaire and Victoria Bowel Performance Scale (BPS) [**Appendix 5**]
- j. ECG
- k. Urine Analysis
- l. Review study product compliance
- m. Dispense a stool collection kit for collection of a stool sample within the 3 days prior to the Week 16 visit. (Note: Subjects should be instructed to freeze the sample in their home freezer immediately after collection and bring the sample frozen to the clinic at their next visit)

9. Visit 8 (Week 16)

The following procedures will be completed at Visit 8:

- a. Review interim medical history
- b. Collect vital signs, weight, and BMI
- c. Review of concomitant medications
- d. Non-directed review of adverse events
- e. Complete **optional** FACIT D&AD Questionnaire and Victoria Bowel Performance Scale (BPS) [**Appendix 5**]

- f. Delivery of a frozen stool sample collected during the prior 3 days to clinic staff
- g. Blood sample collection (**fasting samples**) for the following assessments:
 - (i) Fasting plasma glucose and insulin
 - (ii) Total cholesterol, TGs, LDL, and HDL cholesterol

In addition to the visits to the clinical study site outlined above, all subjects with email and/or text messaging capability will receive an electronic message from their respective clinical study site every second week, starting on Week 4 and ending on Week 10, to remind the subjects which bottle of study product they should be using at that time point and remind them to contact the clinical site with any problems or complaints. The message on Weeks 4, 12, and 16 will be sent 4 days prior to the subjects' upcoming visit to remind the subjects to collect their stool samples and bring them to their next clinic visit.

O. Ethical Safety Considerations:

The overall risk to subjects participating in this study is low. The safety of the microbes in the study product formulations have been demonstrated in rodents studies and a small human safety study. The microbes are all commensal organisms manufactured according to GMP standards using food grade reagents which are GRAS qualified. The manufacturing procedures employ no animal derived products. (See Section I above for detailed discussion.)

Since blood samples will be collected, the risks associated with venipuncture are present.

In addition, while steps have been taken to require no direct contact with stool, the subjects will need to execute the steps required for stool collection and apply the snap-on lid to the collection bucket. In addition, the subjects will need to place the stool collection bucket into their home freezer immediately after collection and keep the collection sample stored frozen until their next clinic visit. While these steps pose little safety risk, some subjects may find this procedure distasteful.

P. Safety Assessments:

Safety will be assessed throughout the study by examination of adverse events (AEs), concomitant medications, clinical laboratory evaluations, vital signs, and physical examinations.

1. Reporting of Adverse Events

Adverse events will be reported in accordance with the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03. The CTCAE grades the severity of the AE based upon Grades 1 through 5 and lists unique clinical descriptions of severity for each AE.

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations

only; intervention not indicated.

Grade 2: Moderate; minimal, local or noninvasive intervention indicated or limiting age-appropriate instrumental ADL.

Grade 3: Severe or medically significant but not immediately life-threatening hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

Grade 4: Life threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

In the event of the occurrence of a same category of three or more grade 3 CTCAE or two grade 4 CTCAE or one grade 5 CTCAE, the trial will be paused, evaluated for safety by the Safety Monitoring Committee and allowed to proceed only after the Committee determines the causality is not associated with the investigational food study product.

2. Adverse Events and Subject Withdrawals

Adverse Event

Any untoward medical occurrence associated with the use of a therapy in humans, whether considered treatment related or not treatment related.

Life-Threatening

Any untoward medical occurrence that places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Serious Adverse Event (SAE)

ANY SAE THAT OCCURS AFTER THE SIGNING OF THE ICF THROUGH 30 DAYS AFTER ADMINISTRATION OF THE LAST AMOUNT OF STUDY MEDICATION MUST BE REPORTED IMMEDIATELY (WITHIN 24 HOURS OF KNOWLEDGE) TO THE SPONSOR'S MEDICAL MONITOR (858-342-7057). FAX THE SAE REPORT FORM TO THE NUMBER LISTED ON THE FORM.

An adverse event is considered "Serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Any SAE, unexpected events, or death encountered during the study and for 30 days thereafter will be reported to the principal and/or co-investigators by the subject (immediately by telephone and subsequently in writing within five (5) days). The investigator will immediately report the SAE/unexpected event or death within 24 hours of being notified to the sponsor for review and assessment/causality confirmation, and to the IRB (per FDA requirements).

Unexpected Adverse Event

An adverse event is considered “unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed.

FDA guidelines recognize that:

1. “Individual adverse event reports generally require an evaluation of their relevance and significance to the study, including an evaluation of other adverse events, before they can be considered an unanticipated problem,” and
2. “All reports to the IRB of unanticipated problems should explain clearly why the event described represents a ‘problem’ for the study and why it is ‘unanticipated.’”

Investigators are required to report unexpected adverse events that fit the following criteria *within 10 working days* of the time the investigator has become informed of the event(s) to both the IRB and sponsor.

The following guidelines provide further definition to unexpected adverse events:

- Event is **unexpected** (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB- approved research protocol and informed consent form or the investigator brochure; and (b) the characteristics of the subject population being studied,
- **Related or possibly related** to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- Suggests that the research **places subjects or others at a greater risk of harm** (including physical, psychological, economic, or social harm) than was previously known or recognized.

If the adverse event is clearly not related to the study food product, device, procedures, or washout process, it would not represent a risk to other subjects in the research or a “problem” for the study and, therefore, does not have to be reported to the IRB.

3. **Intensity**

The intensity of each adverse event will be characterized as mild, moderate, or severe, as follows:

- MILD: Usually transient, requires no special treatment, and does not interfere with the subject’s daily activities.
- MODERATE: Usually causes a low level of inconvenience or concern to the subject and may interfere with daily activities, but is usually ameliorated by simple therapeutic measures.
- SEVERE: Interrupts a subject’s usual daily activities and generally requires systemic drug therapy or other treatment.

4. **Causality**

The investigator will grade the association of the adverse event as UNRELATED or RELATED to study medication. The following criteria should be considered for determining relatedness:

- UNRELATED: The adverse event is judged to be produced by the subject's clinical state or by other therapies administered to the subject.
- RELATED: The adverse event is judged to be related to the administration of study medication.

Q. Blood Volume:

During this study, blood will be drawn for various analytes and panels, including chemistry, hematology, insulin, and inflammatory markers. The total amount of blood to be drawn (during the entire study) is expected to be ~120 mL, which is equivalent to 4 ounces, or 0.3 pints for each subject.

R. Data Management:

All data collected will be entered into electronic Case Report Forms (eCRFs) built upon the OpenClinica platform. The eCRFs enter the collected data into a database that will allow summaries and the statistical analyses outlined in the statistical analysis plan to be conducted.

Upon conclusion of the study, all materials, including a copy of the final, locked electronic database, will be archived.

S. Statistical Considerations:

Analysis Populations:

- **Intent-To-Treat (ITT):** The ITT Population will include all randomized subjects who receive at least one portion of randomized study product, i.e. Placebo (WBF-0009), WBF-0010, or WBF-0011.
- **Evaluable:** The evaluable population will include all ITT subjects who have had adequate exposure to the randomized study product during the 12-week treatment period (Day 0/Visit 1 to Week 12/Visit 7) and have adequately complied with the protocol as assessed by the investigator and sponsor prior to database lock. Additional subjects may be excluded from the evaluable population based on a clinical review of the data prior to database lock with the reason(s) for exclusion recorded. The final definition of the evaluable population will be documented in the prospectively developed statistical analysis plan (SAP), which be submitted for IRB review prior to database lock.

Statistical Analyses:

- **Primary Safety and Tolerability Endpoint:** The primary safety and tolerability endpoint is the incidence of all treatment-emergent adverse events.
- **Primary Efficacy Endpoint:** The primary metabolic efficacy endpoint for the study is the change from baseline to Week 12 in the area under the glucose curve ($\Delta\text{AUC}_{\text{glucose (0-180)}}$) during a standardized 3-hour meal tolerance test (MTT). The primary inflammation efficacy endpoint for the study is the change from baseline to Week 12 in CRP.
- **Secondary Endpoints:**
 1. Assessment of change in the area under the insulin curve ($\Delta\text{AUC}_{\text{insulin}}$) from baseline to Week 12 during standardized meal tolerance test
 2. Assessment of change in fasting glucose from baseline to Weeks 4, 12, and 16
 3. Assessment of change in fasting insulin from baseline to Weeks 4, 12, and 16
 4. Change in hemoglobin A1c from baseline to Weeks 4 and 12
 5. Change in inflammatory markers from baseline to Weeks 4 and 12:
 - a. C-reactive protein (CRP)
 - b. IL-6
 - c. TNF- α
 6. Change in additional inflammatory markers from baseline to Week 12:
 - a. IL-10
 - b. TGF- β
 7. Assessment of change in homeostatic model assessment for insulin resistance (HOMA-IR)

from baseline to Week 12 (<https://www.dtu.ox.ac.uk/homacalculator/>)

8. Assessment of change in the Matsuda index from baseline to Week 12 [Formula for Matsuda index: $ISI(comp) = 10,000 / \sqrt{[(G_0 \times I_0)(G_{mean} \times I_{mean})]}$, where
 - G_0 – Fasting glucose concentration (mg/dl)
 - I_0 – Fasting plasma insulin concentration (mIU/l)
 - G_{mean} – Mean plasma glucose concentration during OMTT (mg/dl)
 - OGGT – oral glucose tolerance test
 - I_{mean} – Mean plasma insulin concentration during OMTT (mIU/l)
 - 10,000– Simplifying constant to get numbers from 0 to 12
 - $\sqrt{}$ – Correction of the nonlinear values distribution
9. Assessment of change in fasting lipid panel [total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides (TGs)] from baseline to Weeks 4, 12, and 16
10. Change in body weight from baseline to Weeks 2, 4, 12, and 16
11. Change in BMI from baseline to Weeks 2, 4, 12, and 16
12. Change in waist circumference between baseline and Week 12
13. Change from baseline in fecal microbiome at Weeks 4, 12, and 16
14. Change in responses to Hospital Anxiety and Depression Scale (HADS) questionnaire from baseline to Week 12
15. Change in response to FACIT D&AD and Victoria Bowel Performance Scale Questionnaire

Both primary and secondary efficacy endpoints will be summarized by treatment and by visit. A detailed Statistical Analysis Plan will be created and submitted to the IRB prior to database lock and unblinding of the data.

T. Safety Analyses:

All reported terms (investigator descriptions) for AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). Treatment Emergent Adverse Events (TEAEs) are defined as adverse events with an onset or worsening after the first amount of study food product. Number and percentage of subjects with TEAEs will be summarized by system organ classification, and preferred term. AEs occurring prior to receiving the first amount of study food product (i.e., during the Screening period) will not be summarized but will be listed.

TEAEs leading to discontinuation from the study, TEAEs possibly or probably related to study food product, serious TEAEs, death, TEAEs by severity (or intensity), and TEAEs with maximum severity (or intensity) and causality, will be summarized.

Additionally, TEAEs of special interest, i.e., specific gastrointestinal symptoms, will be summarized separately, if deemed necessary.

All vital signs, clinical chemistry, and hematology results will be listed by subject and visit, including scheduled and unscheduled/repeat measurements. Laboratory assessments that are outside of normal ranges and/or with potential clinical importance will be flagged. Baseline values, the values at each visit, and changes from baseline values will be summarized descriptively for each of the quantitative laboratory assessments.

U. Sample Size and Power Calculation:

Since this is the initial evaluation of the potential metabolic and anti-inflammatory effects of WBF-0010 and WBF-0011, there are no data to support a formal power calculation. Thus, the sample size is guided by experience and clinical judgement.

V. Investigator and Sponsor Obligations:

1. Medical Supervision

The Investigator will retain subject identification, including subject initials and assigned study number, by attaching a preformatted label to the file copy of the subject's informed consent form, which will be used for long-term follow-up, if needed. This information will also be maintained confidentially by the investigator while sharing only the patient's initials and assigned study number with Sponsor personnel. All other reports and communications relating to the Study will identify subjects by initials and assigned subject number only.

Medical supervision is the responsibility of the investigator named on form FDA 1572. The investigator may delegate day-to-day activities to a sub-investigator listed on form FDA 1572, but retains overall responsibility for ensuring that the study is conducted properly and in accordance with the study protocol. A list will be maintained that includes all qualified persons to whom the investigator may delegate significant study related duties. The investigator is responsible for ensuring that drugs and devices are available for treating possible medical emergencies, or that emergency medical facilities are available and accessible. The investigator is responsible for ensuring that the study is conducted in accordance with GCP, other applicable regulatory guidelines, and sound medical practices.

2. Study Initiation and Discontinuation

Prior to initiation of the study, the investigator must provide the sponsor with the following documents (copies of which must be retained by the investigator in a binder at

the study site):

- Signed original copy of the protocol acceptance statement that commits the investigator to follow the protocol exactly and to conduct the study according to GCP.
- Current curriculum vitae, as indicated by version date in the footer or the investigator's signature and date. Also required is a state license for the investigator and for other medically qualified sub-investigators.
- Signed financial disclosure forms for the investigator and all sub-investigators.
- Signed copy of the IRB approval letter that lists the approved items.
- List of the IRB members who voted on the approval, including their specialty and affiliation, or the IRB assurance numbers if the roster cannot be obtained.
- Copy of the IRB approved ICF(s).
 - Copy of the IRB approved authorization to use and disclose protected health information form, consistent with HIPAA legislation, if applicable.

Upon receipt of all necessary paperwork, the sponsor will arrange for all study materials to be delivered to the clinical study site. The sponsor or designee will train all personnel expected to be involved in the study. This training may include a review of the study protocol, instructions for CRF completion, and a review of overall responsibilities, including study file maintenance.

The sponsor has the right to terminate the study at any time for any of the following reasons:

- Non-adherence of study-site personnel to the protocol or GCP
- Unavailability of the investigator or study-site personnel to the sponsor's monitoring personnel or designee(s)
- Other administrative reasons

Throughout the course of the study, the investigator is to make a reasonable effort to maintain the enrollment rate that was agreed upon with the sponsor. The investigator will also make a reasonable effort to enroll appropriate subjects.

3. **Laboratory Accreditation**

The laboratory facility used for analysis of clinical laboratory samples must provide evidence of adequate licensure or accreditation. Copies of laboratory certification, licensure, and reference ranges (as appropriate) will be supplied to the sponsor prior to study initiation. The sponsor or designee should be notified of any changes in reference range values or certification/license renewal during the course of the study.

4. **Data Reporting**

A CRF must be completed for every subject enrolled in the study. When data are complete, the investigator or medically qualified sub-investigator listed on form FDA 1572 will apply his/her signature on the CRF indicating that he/she has reviewed and approves of the data collected on the CRF.

5. **Study Monitoring**

The investigator will allow qualified sponsor representatives or designee(s) to conduct periodic audits of all CRFs and to review all CRFs and corresponding portions of office, clinical, and laboratory records for each subject at each clinical study site. Reviews of study data will be performed during routine monitoring visits, both during the study and following study completion. These visits are to provide the sponsor with the opportunity to evaluate study progress; verify the accuracy and completeness of CRF; and ensure that all protocol requirements, and investigator obligations are being fulfilled. Finally, any inconsistencies in the study records should be resolved during these visits.

The sponsor may terminate study participation by a clinical study site if study-site personnel do not follow the protocol or GCP. Additionally, individual subjects may be excluded if a medical records review indicates protocol violations or if other factors appear to jeopardize the validity of the study.

The investigator is not to deviate from the protocol. In medical emergencies, the investigator will use medical judgment and will remove the subject from immediate hazard. The investigator will immediately notify the sponsor and IRB regarding the nature of the emergency and the course of action taken. The investigator is to notify the sponsor of any inadvertent protocol deviations upon discovery, and is to document the deviations appropriately in the study files or on the CRFs. The sponsor assumes no responsibility or liability for any unapproved deviations.

Major changes in the protocol initiated by the sponsor will be provided as an amendment and will be approved by the IRB prior to implementation.

6. **Record Retention**

Source documents may include a subject's medical record, hospital charts, clinic charts, procedural records, the principal investigator study files, as well as the results of diagnostic and safety tests.

The PI has the responsibility of maintaining a comprehensive and centralized filing system containing all study-related documentation in accordance with applicable regulations. These files must be available for inspection by the sponsor and regulatory authorities (i.e., FDA) at any time and must consist of at least the

following elements: subject files, containing the completed case report forms (CRFs), supporting source documentation from the medical record including laboratory data and the ICF; regulatory files, containing the protocol with all amendments and investigator signature pages, copies of all other regulatory documentation, and all correspondence between the site and IRB and sponsor; and study food product accountability files, including a complete account of the receipt and disposition of the test article.

The investigator must maintain study documents for a minimum of two years and must obtain written permission from the sponsor before disposing of any study records. If the investigator relocates, retires for any reason or withdraws from the study, the study records may be transferred to an acceptable designee, such as another investigator, another institution, or to the sponsor.

7. **Deviation from the Protocol**

The investigator is not to deviate from the protocol. In medical emergencies, the investigator will use medical judgment and will remove the subject from immediate hazard. The investigator will immediately notify the sponsor and IRB regarding the nature of the emergency and the course of action taken. The investigator is to notify the sponsor of any inadvertent protocol deviations upon discovery, and is to document the deviations appropriately in the study files or on the CRFs. The sponsor assumes no responsibility or liability for any unapproved deviations.

Major changes in the protocol initiated by the sponsor will be provided as an amendment and will be approved by the IRB prior to implementation.

8. **Quality Assurance**

Whole Biome, Inc. may conduct a discretionary quality assurance audit of this study. If such an audit occurs, the investigator agrees to allow the auditor direct access to all relevant documents and to allocate his or her time and that of the study-site personnel to the auditor to discuss findings and any relevant issues. In addition, regulatory agencies may conduct a regulatory inspection of this study. If such an inspection occurs, the investigator agrees to notify Whole Biome, Inc. upon notification by the regulatory agency. The investigator agrees to allow the inspector direct access to all relevant documents and to allocate his or her time and that of the study-site personnel to the inspector to discuss findings and any relevant issues. The investigator will allow Whole Biome personnel to be present as an observer during a regulatory inspection, if requested.

W. Disclosure of Data and Publications:

Subjects' medical information obtained because of this study is considered confidential, and

disclosure to third parties other than those noted below is prohibited. Subject to any applicable authorization(s), all reports and communications relating to subjects in this study will identify subjects only by initials and number. Medical information resulting from a subject's participation in this study may be given to the subject's personal physician, other authorized parties, or to the appropriate medical personnel responsible for the subject's welfare.

Data generated in this study will be available for inspection on request by the FDA or other government regulatory agency auditors, the sponsor, the sponsor's medical monitor (or designee) and its corporate partners for the food study product, if any, and their designated representatives, the IRB, and other authorized parties.

If requested, the investigator agrees to furnish the sponsor with complete subject identification in a confidential disclosure for long term follow-up, if needed. This disclosure will be treated in accordance with applicable law, with strict adherence to professional standards of confidentiality and will be filed by the sponsor with adequate security and restricted accessibility.

All information concerning the study food product and the sponsor's operations (such as patent applications, formulas, manufacturing processes, basic scientific data, or other information supplied by the sponsor and not previously published) are considered confidential and shall remain the sole property of the sponsor. The investigator agrees to use this information only in conducting this study and to not use it for other purposes without the sponsor's prior written consent.

The information developed in this clinical study will be used by the sponsor in the development of WB01 and therefore may be disclosed by the sponsor, as required, to authorized parties (including its corporate partners for the food study product, if any, and their designated representatives), other clinical investigators, the FDA, and other government agencies.

Any information, inventions, discoveries (whether patentable or not), innovations, suggestions, ideas, and reports made or developed by the investigator(s) as a result of conducting this study shall be promptly disclosed to the sponsor and shall be the sole property of the sponsor. The investigator agrees, upon the sponsor's request and at the sponsor's expense, to execute such documents and to take such other actions as the sponsor deems necessary or appropriate to obtain patents in the sponsor's name covering any of the foregoing.

The results of this study may be published under the direction of the sponsor. Results will not be published without the sponsor's prior review and approval.

X. Ethical Considerations:

The study will be conducted in accordance with the Declaration of Helsinki (1964), including all

revisions adopted by the WMA General Assembly through 2013 (Brazil revision), and consistent with good clinical practice and applicable laws and regulations.

The protocol and ICF will be reviewed and approved by a duly constituted IRB before individuals are screened for study entry. The investigator will ensure that all aspects of the IRB review are conducted in accordance with current institutional, local, and national regulations. A letter documenting the IRB approval will be provided to the sponsor prior to initiation of the study. Amendments to the protocol will be subject to the same requirements as the original protocol. The investigator will submit all periodic reports and updates that the IRB may require, including any final closeout reports. The investigator will inform the IRB of any reportable adverse events.

Y. Informed Consent:

Each participant will be provided with oral and written information describing the nature, purpose and duration of the study, procedures involved in the study, participation/termination conditions, and risks and benefits. Prior to initiation of any study-related procedures, subjects will sign and date the informed consent form (ICF) to participate in the study. Subjects will also sign and date an authorization form required under HIPAA, if applicable, that authorizes the use and disclosure of the subject's protected health information. The signed original ICF and HIPAA authorization forms will be retained with the study center's records and each subject will receive a copy of each form they have signed.

Z. Final Report:

All data, including subject characteristics, methodology, and clinical findings, will be presented in a final clinical/statistical report to be prepared by the sponsor or designee.

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Appendix 1

Study Visit Chart
Overview of Procedures

Event	Day -7 to - 14	Day 0	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 16
Phone Visit					x		x		
Consent	x								
Med Hx	x							x	x
Physical Exam		x						x	
Height	x								
Weight	x	x	x	x				x	x
Vitals	x	x	x	x				x	x
BMI	x	x	x	x				x	x
Waist Circum.		x						x	
Con Meds	x	x	x	x	x	x	x	x	x
AEs	x	x	x	x	x	x	x	x	x
Dispense Study Food Product		x	x	x		x			
Stool Samples		x1						x1	x1
MTT (see below)		x						x	
Fasting Glucose	x	x		x				x	x
Fasting Insulin		x		x				x	x
A1c	x	x		x				x	
Fasting Total Chol, TG, LDL and HDL		x		x				x	x
Safety Labs	x	x		x				x	
Inflammatory Markers		x		x				x	
ECG		x						x	
Urine Analysis		x						x	
Questionnaires		x						x	x

For MTT: Glucose and Insulin at T = 0, 30, 60, 90, 120, and 180 min.

Note: Phone visits will be conducted at Weeks 6 & 10 to collect unsolicited, spontaneous adverse events, review conmeds, and access compliance with study product.

Appendix 2

Instructions for Collecting Stool Sample

You will be given a stool collection kit to take home so that you can collect the sample at your convenience. The kit will contain the following pieces:

1. An insulated cooler with ice packs (not shown)
2. A barcoded transparent bag
3. A Stool Collection Device (SCD) consisting of 3 separate components ([Figure 1](#))
 - A. A Stability Frame for positioning the collection bucket on the toilet
 - B. A barcoded Stool Collection Bucket
 - C. A Stool Bucket Lid with a label for recording the date and time of day for the collection
4. Disposable Gloves - 2 pairs
5. Sanitary Wipes
6. Ballpoint Pen

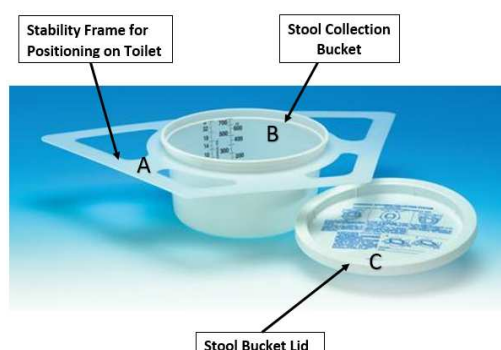


Figure 1: Stool Collection Device

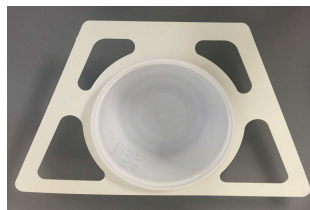
When you get home, please place the cooler (containing the Stool Collection Bucket) into your freezer.

When you are ready to collect your stool sample, take the following actions **in the order listed**:

1. Completely empty bladder.
2. Remove all items from your kit bag and remove the Stool Collection Bucket from the cooler (leave the cooler itself in the freezer) and the transparent bag
3. Use a sanitary wipe to cleanse toilet seat and rim of toilet bowl.
4. Fill out the date (month/day/year) and check the box corresponding to the time of day on the bucket lid label with the provided ballpoint pen.
5. Remove the lid from the bucket and place the lid inside of the transparent bag.
6. Assemble the SCD by inserting the Collection Bucket ([Figure 1B above](#)) securely into the Stability Frame ([Figure 1A above](#)), as shown in [Figure 2](#).

Note: Do not touch the inside of the bucket.

Figure 2: Assembled Stool Collection Device (SCD)



7. Lift the toilet seat and place the SCD horizontally on the edges of the toilet bowl. The narrow side of the frame should face towards the rear end of the toilet bowl ([Figure 3A](#)).

Note: Depending on your personal anatomy, repositioning the narrow side of the frame to face the front of the toilet bowl ([Figure 3B](#)) may better facilitate acquisition of stool sample.

Figure 3A



Figure 3B



8. Lower the toilet seat to secure the SCD ([Figure 4A](#)/[Figure 4B](#)).

Figure 4A



Figure 4B



9. Sit on the toilet and arrange yourself so that the stool sample will fall directly into the bucket.
- Note: Do not urinate or place toilet paper into the Collection Bucket.**
10. When finished, use toilet paper to clean yourself and discard used toilet paper outside of the bucket.
11. Flush the toilet.
12. Then, lift the toilet seat and remove the SCD from the toilet.
13. Set the SCD on a flat surface.
14. Push down on the Stability Frame to detach it from the Collection Bucket.
15. Discard frame.
16. Remove the lid from the transparent bag and push the lid onto the Collection Bucket ([Figure 5](#)). The lid is secure when a “snap” is heard.
17. Place the sealed Collection Bucket into the empty transparent bag and close the bag.
18. Place the closed transparent bag with collected stool sample into the cooler.
19. Store the cooler in the freezer and leave in the freezer until your next clinic visit.
20. At your next clinic visit, bring your cooler (with sample inside) and give to the clinical coordinator.

Figure 5

THANK YOU FOR YOUR PARTICIPATION IN THIS IMPORTANT STUDY!

Appendix 3

Meal Tolerance Test

Overview

A meal tolerance test (MTT) is analogous to the traditional glucose tolerance test. Instead of a large glucose challenge, which is unphysiologic, the MTT employs a standardized mixed meal. In the WB01-202 study, we are using Boost Plus® as the challenge (Caloric content = 720 calories; 50% carbohydrate, 16% protein and 36% fat). Blood samples are taken fasting and at set times from the start of the meal to measure plasma glucose and insulin.

Procedure

1. The subject should not have anything to eat or drink, except for water and the Boost Plus® meal, until the MTT test has been completed.
2. For convenience and comfort of the subject, placement of an indwelling venous sampling device to limit the number of needle sticks required to obtain the blood samples is recommended.
3. Following the instructions regarding which blood tubes to use, included in the self-contained glucose tolerance test (GTT) kit provided by Quest Laboratories, draw the fasting glucose and insulin samples (~5mL of blood): Note: Any other fasting blood samples scheduled for the visit should also be drawn prior to the subject beginning to drink the Boost Plus® liquid meal.
4. Provide the subject with 16 ounces of Boost Plus® (two 8-ounce containers) to drink over 15 minutes.
5. Record the clock time when the subject begins to drink the Boost meal and start a timer to track the time of the subsequent blood samples.
6. Record the time the subject completes ingestion of the Boost challenge.
7. At 30, 60, 90, 120 and 180 minutes following the start of the meal, draw a sample for plasma glucose and insulin following the instructions accompanying the GTT kit as to which blood tubes to use for the samples. Note: If an indwelling venous sampling device is being used, remember to draw and discard an adequate of blood to remove the solution used to keep the device patent between blood draws so that the samples taken are not diluted.
8. After the sample has been taken, if an indwelling sampling device is being used, remember to take the measures needed to maintain patency of the device until the time for the next sample.
9. Record the clock time the sample was drawn.
10. When the 180-minute sample has been obtained, remove the sampling device, if used. The subject can now have anything they would like to eat or drink

11. Follow the established procedures for sending the GTT kit containing the glucose and insulin samples to the laboratory for analysis.

Appendix 4**Hospital Anxiety and Depression Scale (HADS)****Hospital Anxiety and Depression Scale (HADS)**

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over your replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			I feel as if I am slowed down:
3		Most of the time	3		Nearly all the time
2		A lot of the time	2		Very often
1		From time to time, occasionally	1		Sometimes
0		Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			I get a sort of frightened feeling like 'butterflies' in the stomach:
0		Definitely as much	0		Not at all
1		Not quite so much	1		Occasionally
2		Only a little	2		Quite Often
3		Hardly at all	3		Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			I have lost interest in my appearance:
3		Very definitely and quite badly	3		Definitely
2		Yes, but not too badly	2		I don't take as much care as I should
1		A little, but it doesn't worry me	1		I may not take quite as much care
0		Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			I feel restless as I have to be on the move:
0		As much as I always could	3		Very much indeed
1		Not quite so much now	2		Quite a lot
2		Definitely not so much now	1		Not very much
3		Not at all	0		Not at all
		Worrying thoughts go through my mind:			I look forward with enjoyment to things:
3		A great deal of the time	0		As much as I ever did
2		A lot of the time	1		Rather less than I used to
1		From time to time, but not too often	2		Definitely less than I used to
0		Only occasionally	3		Hardly at all
		I feel cheerful:			I get sudden feelings of panic:
3		Not at all	3		Very often indeed
2		Not often	2		Quite often
1		Sometimes	1		Not very often
0		Most of the time	0		Not at all
		I can sit at ease and feel relaxed:			I can enjoy a good book or radio or TV program:
0		Definitely	0		Often
1		Usually	1		Sometimes
2		Not Often	2		Not often
3		Not at all	3		Very seldom

Please check you have answered all the questions

Scoring:

Total score: Depression (D) _____ Anxiety (A) _____










0-7 = Normal

8-10 = Borderline abnormal (borderline case)

11-21 = Abnormal (case)

WB01-202 Subject Optional Questionnaire
FACIT-D & AD (V.4) & Victoria Bowel Performance Scale (BPS)

	Victoria Bowel Performance Scale								
	Constipation			Normal			Diarrhea		
Visit 7/Week 12 (last day of treatment)	-4	-3	-2	-1	G	+1	+2	+3	+4
Visit 8/Week 16 (4 weeks after treatment)	-4	-3	-2	-1	G	+1	+2	+3	+4

- 4		- 3		- 2		- 1		BPS Score G		+ 1		+ 2		+ 3		+ 4	
Constipation				Normal				Diarrhea									
Impacted or Obstructed +/- small leakage	Formed Hard with pellets	Formed Hard	Formed Solid	Characteristics	Formed Semi-solid	Formed Soft	Unformed Loose or paste-like	Unformed Liquid ± mucous	Unformed Liquid ± mucous								
																	
No stool produced after Goal plus 3 days	Goal plus 3 or more days delay	Goal plus 1-2 days delay	Patient's Goal frequency occurs	Pattern	Patient's Goal frequency occurs	Goal or more frequent than goal	More frequent than goal	More frequent than goal									
Unable to defecate despite maximum effort or straining	Major effort or straining required to defecate	Moderate effort or straining required to defecate	Minimal or no effort required to defecate	Control	Minimal or no effort required to control urgency	Moderate effort required to control urgency	Very difficult to control urgency and may be explosive	Incontinent or explosive; unable to control or unaware									

1. BPS is a 9-point scale. It is a **single score**, based on the overall **'best vertical fit'** among the above three parameters [characteristics, pattern, control] and is recorded for example as: BPS +1, BPS -3 or BPS G.
2. Look vertically down each BPS level to become familiar with how the three parameters of **characteristics, pattern & control** change in gradation from constipation to diarrhea.
3. For the bowel pattern, it is the patient's **goal** that is the determining factor. The goal is recorded in the center section, marked with the patient's desired goal for how often they would prefer to have a bowel movement. Based on their goal, then the **actual frequency** is either within that goal, delayed beyond the goal, or more frequent than the goal. If the goal is met, the score is **BPS G**.
4. Patients may use different words than above to describe their bowel activity. One must use clinical judgment in deciding which boxes are most appropriate.
5. For patients with ostomies or short bowel syndrome, **all 3 parameters** should be assessed according to closeness to the patient's desired **goal**.
In potential confounding cases, determination of the most appropriate BPS score is made using the following methods:
 - Two vertically similar parameters generally outweigh the third;
 - Single priority weighting among parameters is Characteristics > Pattern > Control
7. When recording BPS in hospital or facility patient charts where charting is required every shift or daily, a **BPS 'X'** is used to indicate no bowel assessment was done in that timeframe. Otherwise, the actual BPS number is recorded. **Do not write "0"** as it is misleading; the correct recording would be BPS X.
8. The BPS cannot be applied when there is no expected functioning bowel, as may occur with patients on TPN or if imminently dying with no oral intake. If this is the case, the correct recording is **BPS N/A**.

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WB01-202 Subject Optional Questionnaire
FACIT-D & AD (V.4) & Victoria Bowel Performance Scale (BPS)

Please circle or mark one number per line to indicate your response as it applies to the **past 7 days**.

		Not at all	A little bit	Some- what	Quite a bit	Very much
<u>PHYSICAL WELL-BEING</u>						
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4
<u>SOCIAL/FAMILY WELL-BEING</u>						
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	<i>Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box <input type="checkbox"/> and go to the next section.</i>					
GS7	I am satisfied with my sex life	0	1	2	3	4
I						
Subject Initials _____ Subject No. _____		Visit 7 / Visit 8 (circle one)		Date ____ / ____ / ____		

WB01-202 Subject Optional Questionnaire
FACIT-D & AD (V.4) & Victoria Bowel Performance Scale (BPS)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<u>EMOTIONAL WELL-BEING</u>		Not at all	A little bit	Some- what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

<u>FUNCTIONAL WELL-BEING</u>		Not at all	A little bit	Some- what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Subject Initials _____ **Subject No.** _____ **Visit 7 / Visit 8** (circle one) **Date** ____/____/____

WB01-202 Subject Optional Questionnaire
FACIT-D & AD (V.4) & Victoria Bowel Performance Scale (BPS)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	<u>ADDITIONAL CONCERNS</u>	Not at all	A little bit	Some- what	Quite a bit	Very much
C3	I have control of my bowels	0	1	2	3	4
ITF1	I move my bowels more frequently than usual	0	1	2	3	4
ITU2	I am afraid to be far from a toilet	0	1	2	3	4
D1	I have to limit my social activity because of diarrhea (diarrhoea)	0	1	2	3	4
D2	I have to limit my physical activity because of diarrhea (diarrhoea)	0	1	2	3	4
D3	I have to limit my sexual activity because of diarrhea (diarrhoea)	0	1	2	3	4
D4	I am embarrassed by having diarrhea (diarrhoea)	0	1	2	3	4
D5	I have abdominal cramps or discomfort due to my diarrhea (diarrhoea)	0	1	2	3	4
D6	My problem with diarrhea (diarrhoea) keeps/wakes me up at night	0	1	2	3	4
ITF3	I must move my bowels frequently to avoid accidents	0	1	2	3	4
ITF5	I wear pads or protection to prevent soiling my underwear	0	1	2	3	4

Subject Initials ____ **Subject No.** ____

Visit 7 / Visit 8 (circle one)

Date ____/____/____

WB01-202 Subject Optional Questionnaire

FACIT-D & AD (V.4) & Victoria Bowel Performance Scale (BPS)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	<u>ADDITIONAL CONCERNS</u>	Not at all	A little bit	Some- what	Quite a bit	Very much
O3	I have cramps in my stomach area	0	1	2	3	4
ACT11	I have pain in my stomach area	0	1	2	3	4
AD1	Stomach pain interferes with my daily functioning	0	1	2	3	4

Have you noticed any other changes since starting the study?

.....

.....

.....

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.....

.....

~ Thank You ~

Subject Initials _____ Subject No. _____ Visit 7 / Visit 8 (circle one) Date ____/____/____