PARTICIPANT INFORMATION AND CONSENT FORM

Research Project and Title: The Safety and Efficacy of a Probiotic Intervention on SIBO and related gastrointestinal symptoms

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Sponsor: Lallemand Health Solutions (Montreal, Quebec)
Nimble Science (Calgary, Alberta)

This consent form, a copy of which has been given to you, is only part of the process of informed consent. It should give you the basic idea of what the research is about and what your participation will involve. If you would like more detail about something mentioned here, or information not included here, you should feel free to ask. Please take the time to read this carefully and to understand any accompanying information.

RESEARCHER CONFLICTS OF INTERESTS

Andrews occasionally acts as a consultant for the sponsor and has received payments from the sponsor for these services. Dr Andrews is a member of the advisory committee, providing consultation as an expert in meetings with the sponsor in regard to management of the business and affairs of the company. Additionally, Dr. Andrews has an equity interest in Nimble Science.

Because Dr. Andrews has a personal interest in the outcome of the study, it is considered to be a conflict of interest (or possible conflict of interest) by the Health Research Ethics Board of Alberta – Clinical Trials Committee (HREBA.CTC) and requires the study doctor let you know about this in case you have any questions or concerns. In addition to letting, you and HREBA.CTC know about this conflict of interest (or possible conflict of interest), Dr. Andrews has provided a management plan to address any concerns that might arise during the research.

Additionally, Dr. Andrews will not push you to take part in this study over other studies or over standard treatment for your condition and will not prevent you from withdrawing from the study at any time should you so choose. If you ever have concerns about this, you should talk to Dr. Andrews or contact HREBA CTC Toll-Free: 1-877-423-5727.

BACKGROUND/RATIONALE

You have been invited to take part in a research study conducted by Lallemand Health Solutions Inc, a company based out of Quebec, Canada that produces probiotic supplements; and Nimble Science Ltd., a company based out of Calgary, Canada that produces a non-invasive, small, ingestible capsule able to painlessly collect liquid samples from the small intestine. You are invited into this study because you and your physician have reviewed the required inclusion and exclusion criteria and believe that you are eligible to take part.

The gut microbiome is a complex ecosystem within our gastrointestinal (GI) tract. This community of trillions of microorganisms (bacteria, viruses, fungi, and more) plays a key role in maintaining one's overall health. It is known that the small intestine and the bowel may hold information that is of great importance in understanding human health, however to this day, it has remained relatively unexplored, because access is difficult. Studying the composition and associations of this microbial world is essential to gain new insights into human health and may help drive the development of new treatments.

Small intestinal bacterial overgrowth (SIBO) can be defined as the presence of excessive numbers of bacteria in the small intestine, causing gastrointestinal symptoms. These symptoms include bloating, distension (abnormal abdomen shape), diarrhea, abdominal pain, and discomfort. SIBO can be caused by a variety of sources, such as surgery or disease.

It is estimated that 2.5 - 22% of the general population has SIBO. SIBO is currently diagnosed by a bacterial culture of the fluids from the small intestine obtained via endoscopy, or by a breath test (BT) which involves breathing into special tubes at timed intervals after ingesting a sugary drink. Both methods have benefits, but also limitations.

The current treatment for SIBO are antibiotics, determined by the type of bacteria present. However, no clear guidelines exist so it is common practice to use nonspecific antibiotics. Since the use of antibiotics becomes more controlled due to antibiotic resistance, it is critical to search for other effective alternatives to address SIBO while reducing the side effects. Probiotics are live bacteria that have health benefits for humans and offer an alternative treatment option. Particularly, some probiotics, such as the one that will be used in this study, have been shown to help with gastrointestinal ailments such as diarrhea or bloating.

PURPOSE/OBJECTIVES

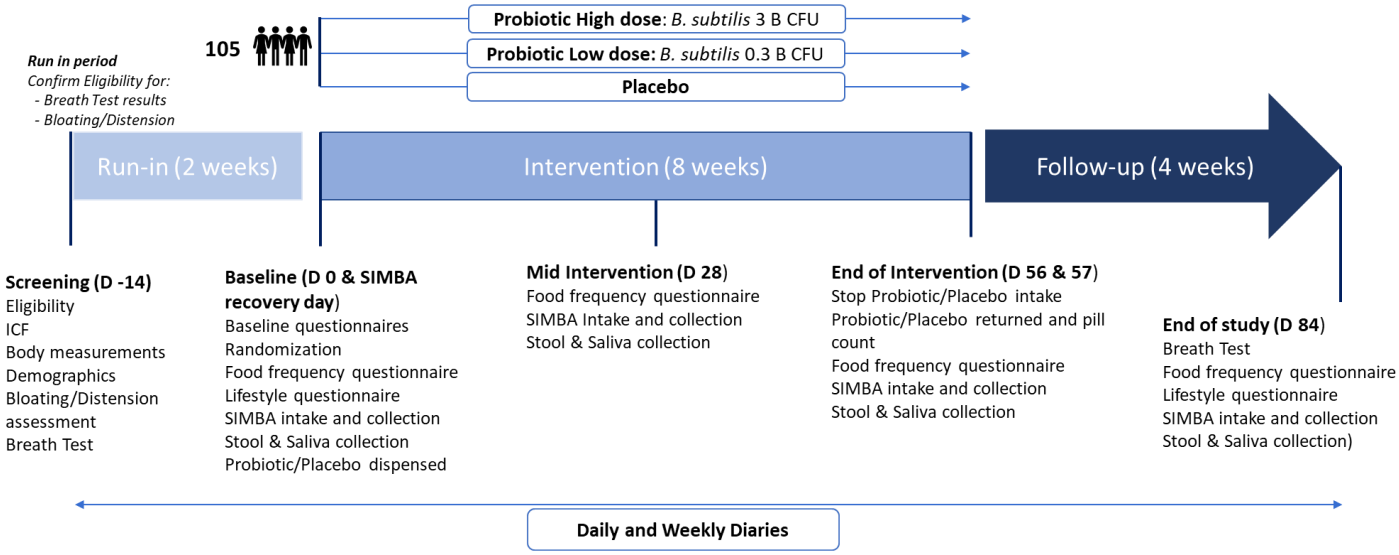
The main goal of this study is to evaluate if 2 different doses of a probiotic product (provided by Lallemand Health Solutions) influence the symptoms of SIBO, particularly bloating, when compared to placebo. Other objectives are to evaluate changes to other gastrointestinal symptoms (discomfort, frequency of bowel movements...); changes in the small intestine and stool microbiome composition (what types of microorganisms are present and in which proportions); change in the quality of life; diagnostic of SIBO by means of a breath test.

To collect samples from the small intestine, the SIMBA Capsule (designed by Nimble Science Ltd) will be used. This device offers a simple, non-invasive, and painless alternative to obtain a sample of the small intestine, suitable for laboratory analysis. The SIMBA capsule consists of a small pill sized container within a specially coated shell and is the size of capsules available in the market for food supplements such as fish oils. When swallowed, the capsule's coated shell (which resists the acidic stomach and dissolves in the small intestine) will pass through the stomach into the small intestine. Once the shell is dissolved, the capsule can collect a fluid sample from the small intestine through the designed openings that are now exposed. Additionally, the small intestinal fluid softens a latch on a spring-loaded plunger which leads to closing the openings and sealing the sampled fluid contents within the container.

STUDY DESIGN

Up to 105 people will take part in this study. Participants will be assigned randomly into the low probiotic dose, high probiotic dose, or placebo groups (35 participants each). In other words, you will have a 33% chance to receive either probiotic low dose, probiotic high dose, or placebo. The study has been designed to participants of a select inclusion and exclusion criteria found. The probiotic tested (the active principle) is *Bacillus subtilis*. Both the probiotic and placebo capsules also include the following excipients: potato starch, magnesium stearate, Hypromellose, and titanium dioxide.

Study Design



The study has been designed to include participants that fulfill a select inclusion and exclusion criteria. You are eligible to participate in this study if you:

1. Are aged 18-55 years old at the inclusion of the study.
2. Sign the Informed Consent and are willing and able to comply with study procedures.
3. Are willing to maintain your diet and physical activity levels during the study.
4. Are able to swallow a size-00 capsule (23mm length and 8mm width).
5. Meet the diagnostic criteria (Rome IV) for functional abdominal bloating distension, functional diarrhea, or IBS-D
6. Meet the criteria for bloating severity.
7. Meet the diagnostic for SIBO as measured with the Glucose Breath Test.

You will not be eligible to participate in this study if you:

1. Have had prior gastrointestinal disease, surgery, or radiation treatment which, in the Investigator's opinion, would lead to intestinal structuring or obstruction with a risk of capsule non-excretion (e.g., achalasia, eosinophilic esophagitis, any IBD), or previous esophageal, gastric, small intestinal, or colonic surgery. Appendectomy or cholecystectomy more than 3 months before the on-site study visit is acceptable.
2. Have any known structural gastrointestinal abnormalities such as structures or fistulas leading to mechanical obstruction.
3. Patients with central venous catheters.
4. Have any history of abdominal radiation treatment.
5. Have used any medications in the week prior on-site study visit, unless part of regular treatment, that could substantially alter gastrointestinal motor function (e.g., opioids, prokinetics, anticholinergics, GLP-

1 analogues); laxative use is allowed if it is kept unchanged in the week prior to the study visit. Proton pump inhibitors (PPIs) are allowed provided a wash-out period of 48 hours is respected before swallowing the SIMBA capsules and PPI treatment is resumed only 4 hours thereafter.

6. Suffer from organic motility disorder, including gastroparesis, intestinal pseudo-obstruction, systemic sclerosis, Ogilvie's syndrome.
7. Suffer from celiac disease (treated or untreated),
8. Have any significant heart, liver, lung, kidney, blood, endocrine or nervous system disease, which in the opinion of the investigator, would adversely affect study safety or outcome.
9. Have had a cancer diagnosis or treatment within the past year (non-melanoma skin cancers are acceptable).
10. Suffer from gastrointestinal inflammatory diseases, including ulcerative colitis, Crohn's disease, microscopic colitis.
11. Participants with IBS presenting with alarm symptoms such as: rectal bleeding, unexplained weight loss, iron deficiency anemia, nocturnal symptoms, and a family history of organic diseases including colorectal cancer, inflammatory bowel disease and celiac spruce
12. Participants over the age of 50 who have not had a colonoscopy in the last 5 years.
13. Have epilepsy diagnosis.
14. Have a history or diagnosis of immunological diseases, infectious diseases or immune-compromised conditions, which in the opinion of the investigator, would adversely affect study safety or outcome. Such as, but not limited to, hepatitis, tuberculosis, HIV, Parkinson's, multiple sclerosis, AIDS, lymphoma, and long-term corticosteroid treatment.
15. Have a history of oropharyngeal dysphagia, or other swallowing disorder with a risk of capsule aspiration.
16. Have a diagnosis of IBS-C.
17. Have used antibiotics (except for topical use) in the previous 12 weeks. You may be eligible to participate once a 12-week washout is completed.
18. History of less than 3 bowel movements per week.
19. Regular use of probiotics, prebiotics or synbiotics (including food and drinks containing added probiotics and/or probiotic yogurts with live, active cultures). You may be eligible to participate once a 1-month washout is completed.
20. Have had a Fecal Microbiota Transplantation at any time in the past.
21. Currently pregnant or breastfeeding.
22. Are planning to become pregnant.
23. Suffer from alcohol or drug abuse.
24. Allergy to the components present in the probiotic and placebo capsules.
25. Are non-English speaking.
26. Are scheduled for an MRI at any time during the study. Potential participants may be eligible to participate once their MRI procedure is completed.

If you suffer from consistent and severe fever, vomiting, bloody diarrhea or abdominal pain, please indicate so to the investigator at any time during the study. The investigator will evaluate whether it is safe for you to continue in the study.

USE OF PLACEBO

What is a placebo?

A placebo is an inactive substance; it has no medication (drug) in it. It looks the same as the real medication.

Why is a placebo used in this study?

In a research study, it is important to obtain accurate information. Many people who have abdominal bloating distension, functional diarrhea, or IBS-D, experience symptoms such as discomfort, pain, altered bowel habits, and psychological distress. A placebo is used in order to "blind" the study so neither you nor the study doctor will know whether you are on active drug. This is done so that you and your study doctor will not be influenced by expectations of the effects of the drug.

What will I give up if I receive placebo?

As previously mentioned, there are a number of treatments available for the treatment of abdominal bloating distension, functional diarrhea, or IBS-D. If you choose to participate in this study, there is a 1 in 3 chance you will receive placebo. This will lengthen the time before you receive a treatment that may be effective. During this time, you may experience worsening of your condition, including increased symptoms such as discomfort, pain, altered bowel habits, and psychological distress. If your symptoms worsen and make you uncomfortable, you can withdraw from the study. You can do this at any time during the study.

STUDY PROCEDURES

How Long Will You Be In This Study?

This study is expected to require up to 14 weeks from when the consent forms are signed until the last planned visit. The study will comprise the following periods and events:

- Run-In period (Day -14 to Day 0)
    - Screening Visit (no more than 14 days prior to the baseline)
- Intervention Period (Day 0 to Day56)
    - Baseline (Day 0, Day 1)
    - Mid-Intervention (Day 28)
    - End of Intervention (Day 56)
- Follow-up Period (Day 56 to Day 84)
    - End of Follow-up (Day 84)

Your participation will be considered complete after the final follow-up call, which will be scheduled within 28 days after the End of Intervention. More details about the visits are mentioned below.

What Will You Be Asked To Do?

This study will be conducted remotely, you will not be required to attend any in-clinic visit. Materials and instructions for the study procedures will be sent to you to an address of your choice, and visits with the researchers will be conducted online or by phone. The diagram below summarizes the general workflow of the study and your participation throughout it.

RUN-IN PERIOD

Screening Visit (Day -14) - Up to 60 minutes.

Before starting any study procedure, we will review the eligibility criteria and the study and answer any questions that you may have. You will then proceed to sign the informed consent if you decide to participate. Once you have consented, demographic information and medical history information will be collected. When applicable, details about your menstrual cycle will also be collected and recorded. We will then confirm bloating diagnosis and IBS status using Rome IV criteria, a standard diagnostic question set. In addition, a urinary pregnancy test will be conducted, if applicable to confirm that you are not pregnant.

In addition, your shipping address for study supplies and materials will be confirmed. Once the shipping address is confirmed, you will receive a Breath Test kit.

Throughout the entire study (from first to last visit), you will be asked to complete a daily diary to collect different aspects as the study progresses. Diaries for each period will be sent to you by email through a platform called Greenlight Guru Clinical. Starting at Screening, and during the run-in period, the following information will be collected:

- Daily assessment of bloating sensation.
- Daily assessment of abdominal pain sensation.
- Stool frequency and form.
- Any medication or supplements taken.
- Menstrual cycle (if applicable).

It is important that, throughout the study, you inform us of any new medication or supplement that you take. We will ask you to record this information in the diary or advise the study team if you have any questions about it.

At this stage, you will then initiate a 2-week run-in period. Immediately upon reception of the kit, you are expected to self-administer and ship off your Breath Test according to the instructions provided.

Run-in activities

This run-in period is meant to confirm the eligibility criteria, mainly your bloating status as well as the breath test results. It is important that the bloating/distension severity assessment is completed within 7 days after the

screening visit and if delayed, before the 14-day screening period ends. In parallel, the study physician will wait for your breath test results.

If your eligibility criteria are confirmed, a baseline visit will be schedule and you will receive a package containing your study materials for this visit. In preparation for baseline, you will have to fast overnight prior to this visit.

At this stage, you will be randomized into one of the study arms. Neither the study physician nor you will know to which group you have been assigned, but the study physician can find out if it is needed.

INTERVENTION PERIOD

During this period, you will be asked to daily take one capsule of the tested supplement. In addition, from baseline to end of the intervention, you will be asked to continue to complete the daily diary, which will include the following aspects:

- Daily questionnaires – up to 10 minutes:
    - Daily assessment of bloating sensation.
    - Daily assessment of abdominal pain sensation.
    - Stool frequency and form.
    - If you have taken the tested supplement (once the intake starts).
    - If you have experienced any adverse effects.
    - Any medication or supplements taken.
- Weekly questionnaires – up to 15 minutes:
    - General gastrointestinal symptom severity.
    - General quality of life.
    - Acid reflux presence and severity.
    - IBS symptoms.

<u>Baseline Visit (day 0) – Up to 45 minutes</u>

Prior to baseline visit, the following materials and instructions will be sent to you:

- 1 set of 2 SIMBA capsules and ingestion instructions.
- 1 bottle of tested supplement and ingestion instructions.
- SIMBA capsule retrieval kit, stool, and saliva collection materials and instructions.
- Sample pickup/delivery instructions.

You will be asked to ingest one set of SIMBA capsules and collect a saliva sample on the morning of day 0. A study coordinator will follow-up with you by phone call to ensure the capsule ingestion was successful.

In addition, you will be asked to complete the following questionnaires, digitally, through the same platform as the diary (Greenlight Guru Clinical – up to 30 minutes):

- Food Diary (3-day retrospective)
- Lifestyle Questionnaire

- Diet History Questionnaire
- Lifestyle Questionnaire (different from General quality of life)
- Bowel Habits Questionnaire (different from the daily stool frequency and form)
- Demographics Questionnaire
- Medical History Questionnaire

In the next days, it is important that you search for the SIMBA capsules when a bowel movement occurs. The capsules may arrive in the same bowel movement or in separate bowel movements. Once you identify the first SIMBA capsule(s), you will be asked to collect the following:

- The SIMBA capsule(s)
- 1 stool sample

If the second SIMBA capsule is found, please collect it as well. Otherwise, please continue to search until it is recovered. You will be asked to record the date and time of the sample collections in your study diary.

Intervention (day 1) – Start of probiotic ingestion schedule

The day after the baseline samples have been collected, you will start to take the tested product. We ask you to take the supplement each day in the evening, during dinner, for a total duration of 8 weeks. If you miss a capsule, please take it as soon as you remember, with a limit of 1 capsule per day.

Mid-intervention check-in (Day 28) - up to 60 minutes

Prior to this visit, you will receive a second kit containing:

- 1 set of 2 SIMBA capsules and ingestion instructions.
- SIMBA capsule retrieval kit, stool, and saliva collection products and instructions.
- Sample pickup/delivery instructions.

In preparation for this visit, you will have to fast overnight prior to this visit. You will be asked to ingest one set of SIMBA capsules and collect a saliva sample on the morning of day 28. In addition, you will be asked to complete a 3-day retrospective food diary.

As during baseline, you will search for the SIMBA capsules when a bowel movement occurs until it is identified. Once identified, you will be asked to collect the following:

- 1 set of SIMBA capsules
- 1 stool sample

End of intervention (Day 56) – up to 45 minutes

Prior to this visit, you will receive a third kit containing:

- 1 set of 2 SIMBA capsules and ingestion instructions
- SIMBA capsule retrieval kit, stool, and saliva collection products and instructions
- Sample pickup/delivery instructions.

Day 56 will be the last day that you will take the tested product. In preparation for this visit, you will have to fast overnight prior to this visit.

The next morning, on day 57, you will be asked to ingest one set of SIMBA capsules and collect a saliva sample. In addition, you will be asked to complete a 3-day retrospective food diary.

As in the previous visits, you will search for the SIMBA capsules when a bowel movement occurs until it is identified. Once identified, you will be asked to collect the following:

- 1 set of SIMBA capsules
- 1 stool sample

In addition, you will be asked to complete the following questionnaires, digitally, through the same platform as the diary (Greenlight Guru Clinical) – up to 15 minutes:

- Medical history questionnaire
- Lifestyle questionnaire (different from General quality of life)
- Diet history questionnaire
- Bowel habits questionnaire (Different from the Daily Bowel Habits)

At this timepoint, we will ask you to return the supplement bottle with any remaining pills, following the shipping instructions provided for the study.

FOLLOW-UP PERIOD

During this period, we will ask you to continue completing a Follow-up diary, which will include the following aspects:

- Daily questionnaires – up to 10 minutes:
    - Daily assessment of bloating sensation.
    - Daily assessment of abdominal pain sensation.
    - Stool frequency and form.
    - Any medication or supplements taken.
- Weekly questionnaires – up to 15 minutes:
    - General gastrointestinal symptom severity.
    - General quality of life.
    - Acid reflux presence and severity.
    - IBS symptoms

<u>Follow-up (Day 84) – up to 45 minutes</u>

Prior to this visit, you will receive a fourth kit containing:

- 1 set of SIMBA capsules and ingestion instructions
- 1 Breath test kit
- SIMBA capsule retrieval kit, stool, and saliva collection products and instructions

- Sample pickup/delivery instructions

In preparation for this visit, you will have to fast overnight prior to this visit. You will be asked to ingest one set of SIMBA capsules and collect a saliva sample on the morning of this day. In addition, you will be asked to complete a 3-day retrospective food diary and the lifestyle diary. We will also ask you about your general experience about the tested supplement and the use of the SIMBA capsule.

As in the previous visits, you will search for the SIMBA capsules when a bowel movement occurs until it is identified. Once identified, you will be asked to collect the following:

- 1 breath test sample
- 1 set of SIMBA capsules
- 1 stool sample

This will mark the end of your participation in the study. Once this study has concluded there will be no follow-up tests associated with this study. If something is found during the course of this research, the information will be given to you, and you can follow up with your physician for appropriate follow-up care. This study does not replace your standard care.

WHICH ARE THE STUDY PROCEDURES THAT YOU WILL FOLLOW AT HOME?

At home Protocol - Tested Supplement Ingestion

The supplement will be taken in the evening, with your dinner. You will be asked to ingest 1 capsule of the tested supplement, with a glass of water, during this meal.

At home Protocol – SIMBA Capsule Ingestion

There are four timepoints in which a capsule set ingestion is required:

- Baseline (Day 0)
- Mid-intervention (Day 28)
- End of intervention (Day 57)
- Follow-up (Day 84)

The instructions for ingestion are as follows:

- On the night before your scheduled ingestion, you will complete an overnight (8 hour) fast of food and liquid.
- On the day of the capsule ingestion (days 0, 28, 57 and 84), you will:
    - Drink 500 ml of water as soon as you wake up.
    - 30 min later you will ingest 2 SIMBA capsules with 250 ml of water.
    - You can then resume your normal schedule and activities but refrain from consuming drinks for 2 hours and food for 4 hours.

- You will receive a call from one of our study coordinators following your ingestion day to ensure capsule ingestion was successful and answer any questions you may have.

At Home Protocol – Capsule Retrieval

Once a SIMBA capsule is identified, you will record date and time in the diary.

- Using the equipment and instructions provided, you will collect the capsules, stool, and saliva samples. Collection of the stool and saliva samples are only needed upon the retrieval of the first capsule. It is possible that the capsules will be excreted at different times. You will be asked to follow the instructions for retrieving the capsule and call the number listed in your take home kit once both capsules are retrieved, unless told otherwise by the study team.
- If you have not retrieved your capsules 5 days following ingestion, you will be contacted by the Nimble Science clinical team to conduct a wellness check.
- If you have any concerns at any point prior to capsule collection, you can contact the study team
- You will receive guidance from the study team. If capsule excretion is delayed, you will be given the option to discuss the next best course of action (standby, laxative, x-ray)
    - If you do not display symptoms (ie. Abdominal pain) the capsules will have been assumed lost and no further action is required.

At-Home Protocol – Breath Test

There are two periods in which a breath test is required.

- Run-in/Baseline (Day 0)
- Follow-up (Day 84)

The instructions to conduct the breath test are as follows:

- On the day before sample collection (Day 0 and 84) you will be instructed to eat a bland diet with minimal fiber or lactose contains foods
- You must fast for 12 hours prior, avoiding all food and drink except water and essential medications.
- The kit comes in a prepaid, pre-addressed box which will be delivered by Canada Post.
- On the day of your breath test you will:
    - Drink 15 mL of lactulose and glucose substrate.
    - Following the kit instructions, you will start a breath sample at baseline and every 20 minutes out to 3 hours, totaling 10 breath samples.
    - Follow the kit instructions for storage and delivery.

What Will Happen When I Have Completed The Study?

Your participation in the study will end after the Follow-Up on Day 84. There will be no further procedures associated with this study.

WHAT IF RESEARCHERS DISCOVER SOMETHING ABOUT ME?

During the study, the researchers could learn something about you that they didn't expect. For example, the researchers may find out that you have another medical condition. The researchers will consult with medical experts as needed to evaluate the findings and will then share these results with you. You will be helped with arranging appropriate follow-up and care.

I consent for the researchers to share findings with me:

☐ YES
☐ NO

RISKS AND DISCOMFORTS

Are There Any Potential Risks Or Discomforts That I Can Expect From This Study?

Taking part in this study has risks. Some of these risks we know about. There is also a possibility of risks that we do not know about and have not been seen in humans to date. Please call the clinical study coordinator if you have any side effects even if you do not think it has anything to do with this study.

What Will Happen If I Miss Or Lose A Simba Capsule?

You can be provided with up to 2 additional sets of SIMBA capsules for missed or lost SIMBA capsules. However, this is an optional choice, it is not mandatory. If you require more than 2 sets of SIMBA capsules, then the researchers will discuss with you your participation in the study, this could result in you being removed.

Risks related to Probiotic

The tested probiotic has been used in over 70 clinical studies, with more than 6000 participants. There have been no serious adverse events reported to date. This means the chance of getting severely ill from the probiotic is very rare.

There exists a low chance of mild risks associated with probiotics, they may upset the gastrointestinal tract such as diarrhea, or flatulence (passing gas) and bloating for the first few days after starting to take them. There are certain people who need to use caution when using probiotic supplements. There is a risk of infection in some people. The inclusion and exclusion criteria are designed to exclude those with higher risk of serious reactions.

If you are allergic to any of the ingredients in the study supplement, you may have symptoms within a few minutes to two hours after taking the supplement. Food allergy symptoms include tingling or itching in the mouth, hives, swelling of the lips, tongue or other body parts, stomach pain, diarrhea, or lightheadedness. If this happens, you should stop taking the product and let the study coordinator know. If you have a severe reaction, seek medical attention immediately.

Risks related to the questionnaires, interview, and medical review

There are no medical risks to the questionnaires, interview, and medical review. Some questions—especially those asked about your mental health—may be uncomfortable or you may feel embarrassed. You may refuse to answer questions at any time if you are uncomfortable.

Risks related to the Breath Testing

The breath test procedure has no risks, but there is a low chance that the ingestion of the test sugar may result in minor abdominal discomfort.

Risks related to Stool Sampling

Collecting stool samples has no risks, but it may feel cumbersome and repulsive, for example that you will have to scoop out part of your stool and return it with your capsules; however, you will be provided will all necessary materials required to perform the sample collection in the privacy of your home washroom.

Risks related to Saliva Sampling

Collecting saliva samples has no risks, but it may feel cumbersome and repulsive.

Risks related to the SIMBA Device

The SIMBA Capsule is an investigational device, and the study is being used to gather data to evaluate its potential clinical use. The SIMBA Capsule has been used to collect over 700 samples from participants, with many (over 200) collected at the Foothills hospital. There have been no serious adverse events and no instances of retention due to obstruction to date. Based on these studies, and the published literature on capsules used in medical practice that are larger than the SIMBA capsule, a risk analysis is provided.

- The primary risk is an occasional probability for the capsule to be retained for an extended time period (ie > 5 days) due to slow bowel transit in the small bowel and is as little as 0.5 percent of the individuals based on 3 cases in 600 ingestions. In all three incidences this was resolved spontaneously.
- We have limited this risk by excluding participants with factors that would increase the likelihood of retention. In most cases, the retention will resolve spontaneously after a short delay and no side effects or complications would be expected. Occasionally, medications are given to help the passage. In the cases where passage may be blocked, an endoscopic procedure can be used, and in rare cases, surgical resection.
- It is possible that you may experience some mild discomfort when excreting the device, but this will be transient and is not expected to cause any long-term damage. If you are not adequately hydrated, it may take longer for you to pass the capsule and the study duration may be extended.
- If the capsules have not been collected after 5 days, inform your health care provider.
- If capsule excretion is delayed, you will receive guidance from the study team and be given the option to standby, bowel cleanse (e.g. laxative), or enema.
    - If you do not display symptoms (ie. Abdominal pain) the capsules will have been assumed lost and no further action is required.

- The SIMBA capsule is not safe for Magnetic Resonance as there are metal components in it. Therefore, an MRI should not be performed during the period of the capsule ingestion until excretion is confirmed.

REPRODUCTIVE RISKS?

While very unlikely, it is not known if the SIMBA capsule used in this study poses a risk to developing fetuses or to babies who are being breastfed. In terms of the probiotic, they are not usually absorbed when consumed orally, the estimated risk for reaching the fetus is considered minimal to non-existent in healthy women. A recent review of the use of probiotics during pregnancy in human clinical trials has reported the absence of adverse maternal or fetal outcomes associated with probiotics consumption.

If you are of childbearing potential, you will be asked to use contraception during the course of the study. Acceptable methods include contraceptive pills, patches, implants, and injections, intrauterine device (IUD), condoms, tubal ligation, and abstinence, and must have been in use a minimum of two months prior to study screening.

Should pregnancy occur during the study, before or while the study supplement is consumed, or prior to SIMBA Capsule ingestion, you must report this to the study coordinator or study doctor and you will be withdrawn as a participant.

In addition, women who are breastfeeding are not eligible to participate in this study.

BENEFITS

Are There Any Potential Benefits If I Participate?

Although participation in this study may be of no benefit to you personally, it is hoped that what is learned here will be of future benefit to others suffering from the symptoms of and diseases associated with SIBO and the investigation of the association with the small intestine and fecal microbiome.

ALTERNATIVES TO PARTICIPATION

Standard probiotics such as Koppert Microflora Pro, or AOR Probiotic-3-90 capsules, contain the probiotic strain being used in this study. These are accessible at your local pharmacy or grocery store, and do not require a prescription.

Choosing a probiotic outside the study brings uncertainty about its effectiveness and may not have been rigorously tested for your specific health condition. This increases the risk of adverse reactions, as different probiotics can affect individuals differently. Moreover, alternative probiotics lack the monitoring and oversight provided by participating in a clinical trial.

What Other Choices Do I Have If I Choose Not To Participate?

Your decision not to participate in the study, or to withdraw from it, will have no impact on the quality of care

and services to which you are otherwise entitled, or on your relationship with the teams providing them. You are not required to participate in this study. The study doctor will be available to discuss the risks and benefits of other gastrointestinal sampling methods or treatments with you.

CONFIDENTIALITY

Will Information About Me And My Participation Be Kept Confidential?

By signing the consent form you give the investigator and sponsor permission to collect, use and disclose medical records as outlined in this section.

Your personal health information (ex. demographic information, medical history, mental health scores) will be collected as part of the study and is limited to the purposes of the study. Your medical records will not be collected during the study. The researchers will ensure that your private information is kept confidential, unless required by law. Lallemand Health Solutions or Nimble Science will not disclose your participation in this study to your primary care physician on your behalf. Information about you will be handled as confidentially as possible, but there is always the potential for an unintended breach of privacy. The research team will handle data according to the Data Management Plan as outlined below:

The Principal Investigator (PI) and the study coordinator will have access to your identifiable data. Upon enrolling in the study, a study number will be assigned to you as an identifier. All study-related documents and processing of data (research data) will be treated as strictly confidential and this code consisting of numbers/letters will identify you. A master list linking the code to your identifiable information will be kept and maintained in a folder in Nimble Science's secured OneDrive access restricted. Only authorized individuals, under the responsibility of the principal investigator, will have access to this list. You have the right to check your health records and ask for corrections to be made.

Authorized representatives from the Health Research Ethics Board of Alberta – Clinical Trials Committee (HREBA-CTC) and/or Health Canada may look at your identifiable medical/clinical study records for quality assurance purposes. Individuals tasked with reviewing data are within Canada and are held to Canada's privacy laws. An independent Data Monitoring Committee will have access to your non-identifiable data to provide un-biased oversite on the analysis of data and the conduct of the study. All study records will be kept for 25 years.

The data collection platform GG Clinical implements both contractual and technical safeguards, as recommended by the European Data Protection Board (EDPB), to minimize unlawful access and processing of personal data. Such safeguards include storing encryption keys separately from application and data hosting services, following the latest EU guidelines, and limiting access to personal data using industry best-practice access security and encryption mechanisms.

Participants will be emailed a link to access GG Clinical. While the GG Clinical platform is designed to protect your privacy, there are potential risks associated with the collection and storage of personal information. These risks include unauthorized access to data and breaches of privacy. However, the platform employs strict security measures to mitigate these risks. Further, emails containing links to the platform could be intercepted by unauthorized parties, potentially exposing sensitive data. To mitigate these risks, it's important to use secure

email practices, such as enabling two-factor authentication and using strong passwords. If you have any questions or concerns about the use of the GG Clinical platform or the protection of your personal information, please feel free to ask.

How Will My Study Data Be Stored And Shared?

GG Clinical is certified under Information Security (ISO27001) and Quality Management system (ISO9001). All data created by Nimble Science using GG Clinical is owned by Nimble Science, and GG Clinical does not have the ability to view or download your data. The GG Clinical platform will be used to collect and manage study-related data, collecting personal information previously outlined. This information will be used for the purposes of the study only and will be identified only by a participant ID number. The personal and medical information about you will be associated only by the participant ID number and will be kept confidential at all times. All information collected through the GG Clinical platform will be stored securely on private hosting services within Microsoft Azure. These servers are compliant with industry standards for data security and are not accessible by third parties. Data will also be stored in secured files and databases at Nimble Science.

Data collected for this study will be shared with an independent Data Monitoring Committee to mitigate conflict of interest on the conduct of the study and analysis of the results. Data may also be shared with other researchers for future studies that are unknown at this time. Any data shared with other researchers will not include your name or other personal identifying information.

Any biological samples (e.g., small intestine aspirates, saliva and stool) obtained for the purposes of this study (study use and quality assurance) will be transported to Nimble Science Ltd. by courier. Your name will not be on the shipping label. These specimens will not include information that identifies you directly. Once you provide the specimens you will not have access to them. You will have the option to remove them from the study if they have not been processed and analyzed (*see WITHDRAWL FROM STUDY*).

However, you can request the destruction of your biological samples at any time. You may also choose to release your biological samples for future research (see additional consent form); however, this is optional and will not affect your ability to partake in this study.

You will be presented with an optional informed consent which will ask if you would like your specimens to be used in future research. Signing this means that Nimble Science may share your specimens in the future with other researchers or outside institutions, collaborators, and companies. The specimens will be used for research and such use may result in inventions or discoveries that could become the basis for new products or diagnostic or therapeutic agents. In some instances, these inventions and discoveries may be of potential commercial value and may be patented and licensed by Lallemand Health Solutions, Nimble Science, our collaborators, and other companies. You will not receive any money or other benefits derived from any commercial or other products that may be developed from the use of the specimens.

How Long Will Information From The Study Be Kept?

If you decide to take part in the study, you give us permission to use de-identified information about you and share it with the Sponsors and others. This permission continues until the study is over, including the length of time that we must keep records about the study.
The researchers must keep all study records and documents (including the signed Informed Consent Form) for at least 25 years after the completion of the study. Study data are kept indefinitely and securely within GG Clinical until the study owner explicitly requests data deletion. When a deletion request is made, the study-specific database is completely deleted from all GG Clinical production services within 10 days. Any backups of the study data are kept for a maximum of 14 days after the database has been deleted. After this period, project data cannot be recovered in any way. GG Clinical has verified and validated this deletion method for every release.

Data may be shared with other researchers, including other institutions, collaborators or companies for future studies that are unknown at this time. Data transmission will occur in a secure password-protected manner. Any personal identifying information will be removed from your data before it is shared.
Any future use of this research data is required to undergo review by a Research Ethics Board.

Confidentiality on the Study Product

The product being tested (probiotic or placebo), may be under development and may not be available to the general public at the moment. The product (including its packaging) which will be given to you for the purposes of the clinical trial are the property of the manufacturer Lallemand Health Solutions. You undertake to keep the tested product confidential and use the tested product only for the purposes of the clinical study in which you are participating.

Public Information about this study:
ClinicalTrials.gov is a website that provides information about federally and privately supported clinical trials. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, and can be found using the NCT number (NCT06317441). This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

HOW CAN I FIND OUT ABOUT THE STUDY RESULTS?

Once all the data has been collected and analyzed, the results may be written in a paper, reviewed by other scientists who work in the same field and published in a publicly available scientific journal. If so, the organizers of the study will try to publish in a scientific journal that gives free access to participants or provides open access directly. You will not be identified in any publication from this study.

I would like to receive a written summary of the results at the conclusion of the study:

☐ YES
☐ NO

COST TO PARTICIPANTS

The investigational products provided, and the study services provided by Nimble Science Ltd, Lallemand Health Solutions come at the researcher's expense. You are not expected to pay for any study costs, and reimbursements are not expected.

Additionally, you will receive up to two $25 gift cards– totaling $50 dollars, one per each completion of the following procedures: baseline and end of intervention. These will be emailed to the participants at each stage of completion.

COMPENSATION FOR INJURY

It is important that you tell the researchers if you believe that you have been injured because of taking part in this study. An independent Data Monitoring Committee will determine if an injury is study related. The committee is independent from the sponsors and the principal investigator.

For medical expenses incurred due to injury/treatment as a result of participating in the study, Nimble Science and Lallemand Health Solutions will provide comprehensive medical insurance which will cover your expenses.

If you suffer an injury as a result of your participation in this research study, no compensation will be provided to you by Nimble Science Ltd, Lallemand Health Solutions or the Researchers.

You still have all your legal rights. Nothing said here about treatment or compensation in any way alters your right to claim damages.

WITHDRAWAL FROM STUDY

Can I Stop Being In The Study?

Yes. You can decide to stop at any time during the study. Tell the clinical coordinator or study doctor if you are thinking about stopping or decide to stop. They will tell you how to stop safely. If you leave the study, your data can be removed until it has been processed and analyzed. After this time, it cannot be removed but no identifying data will be used, and no future data will be collected for the study. Any decision you make will not result in any penalty or impact on your quality of care.

If the SIMBA capsules have not yet passed into your stool we will offer to monitor until the capsules have been retrieved from the stool or verified to have exited your body. This serves as a safety precaution, and is considered a final virtual visit.

Procedure to Withdrawal from the Study

1. Contact the study coordinator and inform them of your decision to withdraw.
2. The coordinator will complete a form detailing your reasons for withdrawal and study feedback (optional).
3. The study coordinator will inform you if your samples have been processed and analyzed.

- If processed and analyzed, no identifying data will be used and no future data will be collected or processed.
- If not processed and analyzed, the data will be removed, samples destroyed, and no future data will be collected or processed.

Can The Researchers Remove Me From The Study?

The study doctor may end your participation in this study for a number of reasons, such as:

- if your safety and welfare are deemed at risk,
- if you do not follow instructions,
- if you miss scheduled visits
- If the sponsor decides to end the study early.

If you decide to stop being in the study, or are removed from the study, or the study is stopped, the study doctor will ask you to complete an exit telephone interview, for the research team to better understand reasons for your withdrawal. You will also be asked to return the remainder of your study supplement. In addition, if the capsules have not yet passed into your stool we will monitor until the capsules have been retrieved from the stool or verified to have exited your body.

Withdrawal Of Study Data

If you decide to stop your participation in the study, or are removed from the study, or the study is stopped, any processed or analyzed data collected about you up to that point will remain part of the study because withdrawal of data in clinical trials could bias results. The information will be used or disclosed if necessary to preserve the scientific integrity of the study; that study data already integrated into the database will not be withdrawn; that anonymized information will continue to be used.

CONTACT FOR FUTURE RESEARCH

The researchers may contact me in the future to ask me to take part in other research studies.

☐YES
☐NO

WHO CAN I CONTACT IF I HAVE QUESTIONS ABOUT THE STUDY?

The Research Team:

You may contact the Clinical Coordinator at (587) 206-2447 or clinical@nimblesci.com with any questions or concerns about the research or your participation in the study. If you wish to be put in contact with the Primary Investigator, you may do so via this same number and email, or the number listed on the next page.

Ethical Review

If you have any questions abchosout your rights as a research participant, and/or concerns or complaints regarding this research study, you should contact The Health Research Ethics Board of Alberta – Clinical Trials Committee at 780-423-5727 or toll-free at 1-877-423-5727. An REB is an independent committee established to protect the rights of research participants.

In the event of an emergency

If during the study you have an emergency, call 9-1-1 and/or visit the emergency department at your nearest hospital immediately. Please report this incident by contacting the research team by phone at (587) 206-2447 or clinical@nimblesci.com . Please also report the occurrence in your daily diary.

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?

Taking part in this study is your choice. You can choose whether or not you want to participate. Whatever decision you make, there will be no penalty to you.

- You have a right to have all of our questions answered before deciding whether to take part.
- Your decision will not affect the standard medical care you receive.
- If you decide to take part, you may leave the study at any time.

SIGNATURE PAGE:

Your signature on this form means that you have understood to your satisfaction the information regarding participation in the research project and agree to participate as a participant. In no way does this waive your legal rights nor release the investigators, sponsors, or involved institutions from their legal and professional responsibilities. You are free to withdraw from the study at any time without jeopardizing the health care you are entitled to receive. Your continued participation should be as informed as your initial consent. You will be informed in a timely manner if information becomes available that may affect your willingness to continue participating in this study. You should also feel free to ask for clarification or new information throughout your participation. If you have further questions concerning matters related to this research, please contact:

Dr. Christopher Andrews – (403) 592-5015

Dr. Christopher Andrews will be receiving financial compensation from the sponsors of this research protocol for your participation in this study.

If you have questions concerning your rights as a possible participant in this research, please contact the Office of the Health Research Ethics Board of Alberta – Clinical Trials Committee at: 780-423- 5727 or toll-free at 1-877-423-5727.

Participant's name (please print): _____ _____
Date

Participant's signature: _____

Investigator's name (please print): _____ _____
Date

Investigator's signature: _____

Delegate's name (please print): _____ _____
(Optional) **Date**

Delegate's signature: _____
(Optional)

Witness' name (please print): _____ _____
(Optional) **Date**

Witness' signature): _____
(Optional)

A signed copy of this form has been given to you to keep for your records and reference.