



UNIVERSITY OF CALGARY

CONSENT TO PARTICIPATE IN RESEARCH

STUDY TITLE: Exploring the relationship between L-dopa responsiveness and Small Intestinal Microbiome in Parkinson's disease (LENSER).

SHORT TITLE: LENSER

SPONSOR: Nimble Science Ltd. & Weston Family Foundation

INVESTIGATORS: Dr. Davide Martino
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INTRODUCTION

You are invited to participate in a research study conducted at the University of Calgary by Dr. Davide Martino, and associates from the Department of Clinical Neurosciences.

This consent form is only part of the process of informed consent. It should give you a clear idea of what the research is about and what your participation will involve. If you would like more detail about something described in this consent form, or information not included in this document, please do not hesitate to ask. Take the time to read this consent form carefully and to understand any accompanying information. You will receive a copy of this form for your records.

You were identified as a possible participant in this study because **you have Parkinson's Disease.**

Your participation in this research study is voluntary.

BACKGROUND

The microbiome is the collection of all microorganisms (such as bacteria, fungi/yeast, and viruses) that naturally live on our bodies (e.g. skin) and in our bodies (e.g. mouth, airways, small intestines and large intestines).

It is known that the small intestine (or bowel) may hold information that is of great importance in understanding human health though it has remained, to this day, relatively unexplored, because the access is difficult. A better understanding of the small intestine microbiome may help drive the search for new insights in Parkinson's disease or its treatment.

Treatment of Parkinson's disease with oral L-dopa may have limited efficacy in a proportion of patients with this condition. In particular, patients may report a fluctuation in the effect of this medication throughout the day, as well as that the effect of some doses may fail to 'kick in'. A possible reason for this is that the small intestine, where L-dopa is absorbed and enters the bloodstream through which it ultimately reaches the brain, may host specific microbes that digest L-dopa and therefore reduce its absorption. This mechanism could not be easily explored to date because collecting small intestine fluid would require endoscopy, which is costly and invasive.

The SIMBA Capsule (designed by Nimble Science Ltd.) potentially offers a simple and easy alternative to obtain a sample of the small intestine microbiome, suitable for analysis. The SIMBA capsule measures about 25x9mm at the time of ingestion (when it is swallowed), which is similar to commonly self-administered capsules of food supplements such as fish-oil.

When swallowed, the capsule will pass through the stomach into the small intestine where it is expected to collect a sample of the fluid content from the small intestine. This sample may be used for basic research (to discover something), clinical research (to research if a given treatment is effective) or for diagnostic evaluation (to confirm or disqualify a known disease).

The SIMBA capsule consists of a small pill sized container within a specially coated shell. This coated shell is designed to resist to the acidic stomach environment and to dissolve in the small intestine. Once the shell is dissolved, the capsule can collect a fluid sample from the small intestine through the specially designed openings that are now exposed. At the same time, the fluid in the small intestine softens a latch on a spring-loaded plunger that forms part of the capsule. This leads to the plunger closing the openings and sealing

the sampled fluid contents within the container. The sealed container can then be collected by the patient or caregiver with a subsequent bowel movement and returned to the laboratory for analysis.

WHY IS THIS STUDY BEING DONE?

We hypothesize that the presence and the activity of specific microbes in the small intestine could predict how well people with Parkinson's disease respond to oral L-dopa. Using material collected through the SIMBA capsule, we wish to analyze how L-dopa is digested by bacteria in the small intestine, and how much this influences the amount of L-dopa in the bloodstream and the clinical improvement achieved after intake of L-dopa.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Up to 120 people will participate in this study through the University of Calgary.

WHAT WILL HAPPEN IF I TAKE PART IN THIS STUDY?

You will attend our research centre for a study visit. During this visit, you will ingest two SIMBA capsules, complete a number of clinical questionnaires and undergo routine neurological examinations before and after L-dopa intake. You will also undergo 6 blood collections over a period of about 3-4 hours, in between clinical assessments. After the visit, you will be given kits to collect stool at home. You will be asked to collect stool from every bowel movement up to 2 weeks after the visit, and until our laboratory retrieves the SIMBA capsules in one of your stool specimens.

Screening (Up to 1 – 2 hours):

(This may take place over the phone or during a visit at the clinic.)

- We will present the study information to you and review this consent form.
- We will review a part of the inclusion and exclusion criteria to assess if you can participate to the study.
- The screening visit can take place virtually or in-person.
- If you are eligible and elect to participate, we will forward the consent form to you via DocuSign for electronic signature (during a virtual visit) or will give you the consent form for wet ink signatures (during an in-person visit).
- Once you have consented, we will ask you about your medical history and your current treatment and other medications. We will further review your eligibility.
- You may be asked to attend a virtual consultation (call) with the study doctor (principal investigator) to confirm your eligibility (whether you can participate to the study).

- We will review the steps needed to prepare for the on-site study visit which includes advance completion of questionnaires, fasting schedule and timing of your medication intake (if applicable).

Preparing for your on-site visit (approximately 45 min)

- You will be asked to complete a series of questionnaires, including one that collects the most common foods you have consumed over the four weeks leading up to your on-site visit. This should take approximately 30 to 45 min to complete.
- On the night before your scheduled on-site visit, you will avoid eating foods for 8 hours before your scheduled on-site arrival time. This is to make sure you don't have any food in your stomach for the sample collection.
- You will be asked not to take Levodopa medication for 12 hours prior to your scheduled on-site arrival time. You can take controlled-release levodopa before bedtime for nighttime issues.
- You will also be asked not to take any medicine that reduces stomach acid (proton pump inhibitors like Omeprazole) for at least 48 hours before the study visit. This is because of the SIMBA capsule requirements.

On-Site Visit (Up to 7 hours)

(This is an in-person visit at the clinic.)

Clinical assessments and review of exclusion criteria (approx. 30min)

- As detailed above, we will ask you to come to the on-site study visit with an empty stomach (hold off on eating foods for at least 8 hours before the visit). Your Levodopa intake will be timed within the study visit (see below).
- We will review all inclusion and exclusion criteria and assess to re-confirm if you can participate in the study. This will include some clinical assessments.
- You will be asked to do a urine pregnancy test if there is any suspicion of pregnancy, or you are able to become pregnant.

Levodopa intake

We will ask you to not take Levodopa medication for 12 hours before coming to the visit. You can take controlled-release levodopa before bedtime for nighttime issues. We will also ask you to not take any other dopaminergic medications for at least 24 hours before the study visit.

- We will ask you to take two SIMBA capsules (one kit) one hour before (+/- 15 minutes) you take the study standard dose of 200mg levodopa and 50 mg carbidopa to ensure the SIMBA capsules are present in the small intestine at the moment of levodopa inflow.

SIMBA capsule and domperidone intake

- We will provide you with one SIMBA Capsule kit (containing two capsules) and will assist your ingestion of the capsules. The ingestion will start by asking you to drink 500 ml of water. This is to make sure your small intestine is hydrated, which will help us collect better samples.
- After 30 min, you will be asked to take both SIMBA capsules with 250 ml of water, along with a 10 mg tablet of Domperidone. This tablet helps the capsules move smoothly to the small intestine. If you are not able to swallow the SIMBA capsules your participation in the study will be terminated.
- You cannot take proton pump inhibitors (medicines that reduce stomach acid) for 48 hours before and 4 hours after taking SIMBA capsules.
- You will need to withhold from eating for at least 2.5 hours after taking the SIMBA capsules and up to 4 hours.

X-ray assessments(s)

- After you take the SIMBA capsules, you will be asked to do at least one and up to six X-Ray assessment(s). The X-rays will be taken every hour, starting 1 hour after you take the SIMBA capsules. The X-rays will be taken until a capsule is observed to be fully closed in the X-ray image. We will however not do more than six X-rays. The x-rays are necessary to monitor the progress of the capsule, so that researchers will know where exactly in the small intestine it has taken its sample. Once the capsule has been confirmed to leave the stomach you will be able to take your meal.
- We will review your previously collected medical & surgical history, treatment history and demographics.

Blood sampling

- We will collect six blood samples (up to 100 ML in total, about 6 tablespoons).
- The first blood sample will be taken prior to levodopa intake.
- Subsequent blood samples will be taken post levodopa intake, specifically 30, 60, 90, 120 and 180 minutes after.

Questionnaires and stool collection kit

- You will be asked to fill out several questionnaires on bowel habits (10 – 15 min approx.) and diet (1 hour approx.).
- After the blood sampling and the x-ray(s) are completed, you will be sent home with a stool collection kit.
- At the end of the study visit you will be able to resume your normal activities.

At Home Protocol – Capsule Retrieval

- Using the materials and instructions provided in the stool collection kit, you or your caregiver will collect stool samples. It is possible that the capsules will be excreted at different times.
- You will be asked to follow the instructions for retrieving the stool samples and scheduling the provided courier pick up service. This will initiate the pickup for the sample transportation.
- The study team will inform you when both capsules have been retrieved and stool collection can be stopped.
- If you have not passed one or both capsules after 5 days and have had at least one spontaneous bowel movement, you will be offered a laxative or bowel cleanse to accelerate capsule retrieval. This will also be proposed if after 8 days you have not had any bowel movements at all. You will collect all stool following the laxative or bowel cleanse and send the samples to Nimble Science using the provided courier pickup service.
- If you have any concerns at any point prior to capsule collection, contact the Study Coordinator. You will receive guidance from the study doctor.
- If both capsules have not been collected after the use of the laxative or bowel cleanse, you will be invited to the clinic to receive a follow up X-ray to determine if the device has been excreted.

Follow Up (Up to 30 min):

(This may take place over the phone.)

- You will be asked to have a final Follow-Up conversation 2-9 days after the onsite visit to talk with the Study Doctor or Study Coordinator about your experience with the capsules and how you are feeling.

WHAT WILL HAPPEN WHEN I HAVE COMPLETED THE STUDY?

You are considered to have completed the study at the end of your Follow-Up conversation. Once this study has concluded there will be no follow up tests associated with this study.

This study does not replace your standard care.

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

HOW LONG WILL I BE IN THIS STUDY?

This study is expected to take about 2 to 5 weeks to complete, depending on scheduling. Your study will comprise the following three study events:

- Screening period (no more than 28 days prior to the on-site visit)
- On-Site visit (1 day)
- Follow-up call/visit (1 day, max. 9 days after the On-site visit)

Your participation will be considered complete after the final follow-up call/visit, which will be scheduled within 7 days after the On-Site visit. More details about the visits are mentioned above.

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.

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 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.

Risks related to SIMBA Capsule

- 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 500 samples from participants, with many (over 200) collected at the Foothills hospital. There have been no serious adverse events and no instances of retention 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 the possible retention of the capsule in the small intestine, though this is uncommon. 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. In case one or both capsules have not passed after 5 days and at least one spontaneous bowel movement has occurred, a bowel cleanse using laxatives, or an enema may be offered to help the passage. This will also be proposed if no bowel movements have occurred 8 days after capsule ingestion. In the cases where passage may be unsuccessful, an endoscopic procedure can be used, and in very rare cases, surgical resection (0.02% is the reported occurrence for the larger video endoscopy capsules).
- If you experience some mild discomfort post-ingestion (after having swallowed the 2 SIMBA capsules) or when excreting (when bowel movement occurs) the device, it will be transient and is not expected to cause any damage. If you are not adequately hydrated, it may take longer for you to pass the capsule and the study duration may be extended.
- 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.

Risks related to Blood Draw

When you provide (a) blood sample(s), the risks may include bruising, swelling, discomfort, or infection at the site where blood is drawn. Any discomforts experienced will likely be brief and transient.

ARE THERE REPRODUCTIVE RISKS?

While very unlikely, it is not known if the device used in this study poses a risk to developing fetuses or to babies who are being breastfed. If you are of childbearing potential, you will be asked to use contraception during the study.

Female participants

If you are of childbearing potential, you must do one of the following while in the active intervention stage (i.e., from intake of the SIMBA capsules until they are excreted) of the study:

- you must use a medically approved effective method of birth control; or
- you must not have sexual intercourse that could result in pregnancy.

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. In addition, this study may require that you have X-rays during the study.

If you are of childbearing potential, you will be required to take a pregnancy test and the test will have to be negative before taking the SIMBA capsules and undergoing an X-ray.

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

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

ARE THERE ANY POTENTIAL BENEFITS IF I PARTICIPATE?

There will be no direct benefit to you from participating in this study. However, this study will help the researchers learn more about Parkinson's Disease. Hopefully this information will benefit in the treatment of future patients with Parkinson's Disease.

WHAT OTHER CHOICES DO I HAVE IF I CHOOSE NOT TO PARTICIPATE?

You are not required to participate in this study. If you chose not to take part in this study, you will receive the usual standard of care from your medical team.

Participation in this study does not interfere with your current Parkinson's treatment. This study does not replace your standard care.

CAN I STOP BEING IN THE STUDY?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. They will tell you how to stop safely.

If the 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.

CAN THE RESEARCHERS REMOVE ME FROM THIS STUDY?

The study doctor may end your participation in this study for several reasons, such as:

- if your safety and welfare are deemed at risk;
- if you do not follow instructions;
- if you miss scheduled visits.

The study doctor or the study sponsor might also decide to stop the study at any time.

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 (much like the follow-up conversation).

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, the data collected about you up to that point will not be included in the study and will be destroyed.

WILL I BE PAID FOR PARTICIPATING, OR DO I HAVE TO PAY FOR ANYTHING?

You will not benefit financially from participating in this study. However, you will receive \$45 stipend to cover travel and parking for the in-person study visit.

Your Alberta Health Care Insurance Plan will not be billed for any visits, treatments or procedures related to the conduct of this study.

Nimble Science and study personnel are not responsible for the cost of any remedies (prescription or non-prescription) that may be required to treat possible side effects.

WILL INFORMATION ABOUT ME AND MY PARTICIPATION BE KEPT CONFIDENTIAL?

Your personal health information (ex. demographic information, medical history, mental health scores) will be collected as part of the study.

The researchers will ensure that your private information is kept confidential, unless required by law. 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 research staff will have access to your identifiable data. All study-related documents and processing of data (research data) will be treated as strictly confidential and only a 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 secure location at the University of Calgary. Only authorized individuals

will have access to this list. All identifiable information about you will be replaced with a code before the study data is shared with the Sponsor.

Authorized representatives from the University of Calgary and the Conjoint Health Research Ethics Board or Health Canada or the Sponsor (authorized personnel, e. g. study monitors) may look at your identifiable medical/clinical records and your research records for quality assurance purposes. By signing this form, you are authorizing such access.

HOW WILL MY STUDY DATA BE STORED AND SHARED?

Paper records containing study data will be kept in a secured, locked location with restricted access. Some research data and records collected during the study will be stored electronically on a secure network with password protection and will be identified only by a study ID number and an individual code consisting of numbers and letters. Access to the electronic database will be restricted to the research team. The personal and medical information about you will be associated only by the study ID number and individual code and will be always kept confidential.

Your biological samples will be transported to Nimble Science by courier. These specimens will not include information that identifies you directly. Your name will not be on the shipping label. To protect your confidentiality, a pre-printed shipping label is created by Nimble Science Ltd on which a code rather than a name is shown on the shipping label. You may be asked to contact Nimble Science directly for shipping or capsule collection support. You will not be required to provide your name only your Study ID. You can choose to provide your home address or another address of convenience as the pick-up address. This pick-up address will not be disclosed towards the sponsor.

The study investigators will make every effort to maintain the confidentiality of your research records to the extent permitted by law.

HOW LONG WILL INFORMATION FROM THE STUDY BE KEPT?

The researchers intend to keep the research data for at least 15 years after the completion of the study.

Data will be shared between the collaborator Nimble Science Ltd and the University of Calgary laboratories (Dr. Sycuro and Dr. Martino), and 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.

WHAT OTHER THINGS SHOULD I CONSIDER BEFORE PARTICIPATION?

Use of My Biospecimens:

Storage of My Biospecimens

If you consent, the samples will be banked and stored at Nimble and at the University of Calgary, or one of their collaborators for future research. All data and sample transfer will be done under agreements between the University of Calgary and Nimble Science and will be reviewed by the ethics board. Any specimens (e.g., blood, stool and intestinal fluid from the SIMBA capsule) obtained for the purposes of this study will become the shared property of the University of Calgary and Nimble Science. Once you provide the specimens you will not have access to them. Information that identifies you will not be shared with anyone outside of University of Calgary and will not be linked to the specimens. Biospecimens may be kept indefinitely.

Confidentiality

We will protect the confidentiality of your information to the extent possible. All data transferred will be de-identified and will not show who you are. Samples transferred will also not contain any of your identifiable information and will only be attached to your study ID. The code key will be kept in a locked location separate from your information. The code key can only be accessed by people at the University of Calgary who have permission.

Use of biospecimens for future research

The biospecimens 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 the University or Nimble Science Ltd and collaborators. You will not receive any money or other benefits derived from any commercial or other products that may be developed from use of the biospecimens you have provided. Your name and other identifying information will not be on any biospecimens you provide. The biospecimens will have a code that links to your identifying information. The code key will be kept in a locked location, at the University of Calgary, separate from your information.

Conflict of Interest disclosure:

Dr. Joseph Wang (collaborator) from Nimble Science Ltd will receive funding for service provision to execute parts of this project. The data related to the main aims of this research will be generated by researchers at the University of Calgary. There will be no influence of Nimble Science Ltd on the generation of this data.

USE OF DATA AND BIOSPECIMENS FOR FUTURE RESEARCH

It is your choice whether to let researchers share your data and biospecimens for research in the future. If you say “yes,” you can change your mind later, but your data and biospecimens might still be used if they have already been shared.

My de-identified research data and biospecimens may be kept for use in future research to learn about, prevent or treat other health-related problems.

→ YES

→ NO

CONTACT FOR FUTURE RESEARCH

University of Calgary researchers may contact me in the future to ask me to take part in other research studies.

→ YES

→ NO

IF I SUFFER A RESEARCH-RELATED INJURY, WILL I BE COMPENSATED?

It is important that you tell the researchers if you believe that you have been injured because of taking part in this study.

If you suffer an injury as a result of your participation in this research study, no compensation will be provided to you by the University of Calgary, Nimble Science Ltd, Alberta Health Services or the Researchers. However, you still have all your legal rights. Nothing said in this consent form alters your right to seek damages.

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

The Research Team:

You may contact the Clinical Research Coordinator at 587-893-2511 or davide.martino@ucalgary.ca with any questions or concerns about the research or your participation in this study.

Conjoint Health Research Ethics Board (CHREB):

If you have any questions concerning your rights as a possible participant in this research, please contact the Chair, Conjoint Health Research Ethics Board, University of Calgary at 403-220-7990.

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> (NCT06762028). 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 patients 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

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

Taking part in this study is your choice. You can choose whether you want to participate. Whatever decision you make, there will be no penalty to you.

- You have a right to have all your 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.

HOW DO I INDICATE MY AGREEMENT TO PARTICIPATE?

Your signature on this form indicates that you have understood to your satisfaction the information regarding your participation in the research study and you agree to participate. In no way does this waive your legal rights nor release the investigators or involved institutions from their legal and professional responsibilities.

SIGNATURE OF STUDY PARTICIPANT

By signing this consent form, you understand that the research team will have access to your individually identifying health information for research purposes. Since this study involves an intervention i.e. research-related medication and use of a device and includes research-specific lab tests and/or imaging, your signed consent will also be included in your electronic medical record(s), and healthcare staff will know that you are in a research study.

Name of Participant

Signature of Participant

Date (dd-mmm-yyyy)

SIGNATURE OF PERSON OBTAINING CONSENT

Name of Person Obtaining Consent

Contact Number

Signature of Person Obtaining Consent

Date (dd-mmm-yyyy)

SIGNATURE OF THE WITNESS

Name of Witness

Signature of Witness

Date (dd-mmm-yyyy)

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