Title: Evaluating the Effect of Prebiotics on the Gut Microbiome Profile and β-cell Function in Newly Diagnosed Type 1 Diabetes

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INDIANA UNIVERSITY INFORMED CONSENT STATEMENT FOR

Evaluating the Effect of Prebiotics on the Gut Microbiome Profile and β-cell Function in Newly Diagnosed Type 1 Diabetes

Your child is invited to participate in a research study using a prebiotic to see its effects on insulin production and gut bacteria in persons with newly diagnosed with type 1 diabetes. A prebiotic is a special form of dietary fiber that we think will help control your diabetes and help feed the good bacteria found in the gut. Your child was selected to participate because he/she was diagnosed with type 1 diabetes in the past 3 years and is between the ages of 11 and 17 years old. We ask that you read this form and ask any questions you may have before agreeing to your child being in the study. "You" may refer to you or your child throughout this document.

The study is being conducted by Dr. Heba Ismail at Indiana University in the Division of Pediatric Endocrinology. It is funded by the Department of Pediatrics at Indiana University.

STUDY PURPOSE

The purpose of this study is to determine if using a prebiotic has an effect on blood sugars and the amount of stress that is experienced by the body's cells that make insulin. These cells are called beta cells. This prebiotic also has an effect on restoring the balance and composition of bacteria normally living in the intestine. We hope to be able to learn more about whether this prebiotic may be a useful supplement for persons with type 1 diabetes. The prebiotic being studied is not FDA approved, so this is considered "investigational."

NUMBER OF PEOPLE TAKING PART IN THE STUDY:

If your child agrees to participate, he/she will be one of up to 24 participants. This study will last about 12 weeks and involves 5 visits. Each participant will take a prebiotic for 4 weeks along with following the usual diabetic diet recommendations, followed by a 4-week break and then 4 more weeks following the usual diabetic diet recommendation only or vice versa. The prebiotic used is called HAMS-AB.

Everyone is expected to follow the recommended diet during the study, except during the 4-week break. Some children will start with the prebiotic and end with the diet recommendations while others will start with the diet recommendations and end with the prebiotic.

The process of figuring out which your child will start with is called randomization and is determined by chance (like flipping a coin).

PROCEDURES FOR THE STUDY:

If you agree to be in the study, your child will do the following things:

For visits 2, 3 and 5, your child will need to fast. This means he/she cannot eat or drink anything except for water for ten hours prior to the study visit. These fasting visits will need to be scheduled in the morning. We will also measure height, weight, blood pressure, heart rate, and temperature at each visit. We will examine your child as well as check his/her insulin use. At each visit except Visit 1, we will ask your child to collect a stool sample 1-3 days before each visit. We will provide you with stool sample collection kits and instructions.

<u>Visit 1 (Screen): This visit may take up to 2 hours.</u>

Before the study starts, we will talk to you about the study and answer any questions you have. You will be asked to sign this consent form, give your child's health history, medicines he or she takes, and other information needed to determine if your child is eligible. This visit will also include:

- Physical examination by the study doctor.

- Take a blood sample (approximately 1.5 tablespoons) to measure whether your body continues to make some of its own insulin and other markers related to diabetes.
- For female adolescents: urine will be collected for a pregnancy test
    - We will ask you to have a pregnancy test before you start this study. Parents of participants who are less than 14 years old, will be told the result of the pregnancy test. Participants who are 14 years old or older, will only themselves be told the results, but will also be advised on how to get care for the pregnancy including the support of an adult.
    - You will not continue in the study if your pregnancy test is positive.
    - If there is any chance that your child is pregnant or might become pregnant during the time of this study, we would recommend that you think carefully about whether she should participate.
- We will notify you of your child's lab results.
- We will ask about your child's diet to determine if they can participate in the study.
- We will ask your child to try the prebiotic with applesauce or oatmeal to make sure your child will be able to eat the study prebiotic without any problems.
- If we find that your child is continuing to make some of his/her own insulin and meet certain height and weight measurements, he/she will be invited back for the next step. We will provide you with a stool collection kit for the next visit. You will also be provided information on how to fill a diet recall form for the 24 hours prior to the stool sample collected.

<u>Visit 2 (Treatment Start): This visit may take 1-2 hours</u>

This visit will include:

- Asking you about changes in your child's medical history since the last visit, including insulin use.
- A brief physical assessment by the bedside nurse.
- You will also be asked to fill out a diet history questionnaire or provide a diet diary (this can be done prior to the visit).
- For female adolescents: urine will be collected for a pregnancy test
- Taking a blood sample (approximately 2 tablespoons) to measure your blood sugar control and other things about your diabetes.
    - Some of the blood taken from you will be saved for the study doctors to use later. This is optional and you will be asked whether you agree to this at the end of this document.
- We will obtain from you the stool sample collected prior to or the same day as the visit.
- You will be provided with a new stool collection kit for the next visit and logs for logging insulin doses.
- If you are not currently using one, we will then place a continuous glucose monitor (CGM), sometimes also referred to as sensor. You will be asked to wear this for 4 weeks. This CGM will need to be changed after 14 days or if it falls out. You and your child will be trained on how to insert a new CGM. You will be provided with two additional CGMs for this purpose. If using the CGM provided through the study, you will not be able to see the sugar values on this monitor as they are collected but the investigators will be able to access these data when you return the device and they will help the investigator understand if your sugars are affected by taking the treatment.
- A computer program will randomize your child to either taking the prebiotic first twice a day for 4 weeks or not. You will be given a supply to last the 4 weeks and you will be asked to mix it with food such as applesauce or oatmeal. Whether you are randomized to start with the prebiotic or not, current diet guidelines for people with diabetes will be given to you to follow for those 4 weeks.

<u>Visit 3 (After Treatment – 4 weeks after enrollment): This visit may take 2-4 hours</u>

- We will ask you questions about your medical history, including your insulin use and any problems you are having with the medications.
- A brief physical assessment by the bedside nurse.
- We will download the glucose data from the CGM.
- For female adolescents: urine will be collected for a pregnancy test
- You will also be asked to fill out a diet history questionnaire or provide a diet diary (this can be done prior to the visit).

- Take blood samples (approximately 5 tablespoons total including for the mixed meal tolerance test below) to measure your blood sugar control and other things about your diabetes
    - Some of the blood taken from you will be saved for the study doctors to use later. This is optional and you will be asked whether you agree to this at the end of this document.
- Your child will complete a mixed meal tolerance test (MMTT) which involves drinking Boost®. It is like a milkshake, and it will raise his/her blood sugar. The study doctors use this test to determine how much insulin your child's beta cells can make. You will be given specific instructions on insulin dosing and diet for 3 days prior to the MMTT. On the morning of the test, your child may only drink water and will not take short-acting insulin within 2 hours of the test. Your child will also be asked to not exercise 10 hours prior to this test as this can alter his/her blood sugar level. An IV cannula (plastic tube in vein) will be placed in his/her arm for drawing blood. Blood will be drawn from the IV cannula before drinking the Boost®. Your child will be given 5 minutes to drink the Boost®, and then blood will be drawn up to 7 times for 2 hours. The amount of the drink will depend on your child's body weight but will be no more than 12 ounces.
- We will obtain from you the stool sample, your child collected prior to this visit. You will be provided with a new stool collection kit for your next visit as well as insulin dose log sheets.
- You can then take a break from following the recommended diet for the next 4 weeks. If you were taking the supplement in addition, you will stop taking it for the next 4 weeks.

<u>Visit 4 (Cross-over – 8 weeks after enrollment): This visit may take 1-2 hours</u>

This visit includes:

- We will ask you questions about your medical history, including your insulin use and any problems you are having with the medications.
- A brief physical assessment by the bedside nurse.
- For female adolescents: urine will be collected for a pregnancy test
- You will also be asked to fill out a diet history questionnaire or provide a diet diary (this can be done prior to the visit).
- Take blood samples (approximately 2 tablespoons) to measure your blood sugar control and other things about your diabetes.
    - Some of the blood taken from you will be saved for the study doctors to use later. This is optional and you will be asked whether you agree to this at the end of this document.
- We will obtain from you the stool samples your child collected.
- We will provide you with a new stool collection kit for your next visit as well as insulin dose log sheets.
- You will need to restart following the recommended diet. If it is your turn to now start using the supplement, then you will be given a supplement supply at this visit to be taken twice daily for 4 weeks and to be mixed each time with food such as applesauce or oatmeal.
- You will be asked to insert a new CGM at this visit if using the CGM provided through the study. You will need to change the CGM after 14 days, or if it falls out. We will provide you with 2 additional CGMs.

<u>Visit 5 (Post Study Follow-Up) This visit may take 2-4 hours.</u>

This visit includes:

- Physical examination by the study doctor.
- We will ask you questions about your medical history, including your insulin use, and problems taking you are having with the medications.
- For female adolescents: urine will be collected for a pregnancy test.
- You will also be asked to fill out a diet history questionnaire or provide a diet diary (this can be done prior to the visit).
- Take blood samples (approximately 5 tablespoons total including for the mixed meal tolerance test below) to measure your blood sugar control and other things about your diabetes
    - Some of the blood taken from you will be saved for the study doctors to use later. This is optional and you will be asked whether you agree to this at the end of this document.
- Your child will complete a mixed meal tolerance test (MMTT) which involves drinking Boost®. It is like a milkshake, and it will raise his/her blood sugar. The study doctors use this test to determine how much insulin your child's beta cells can make. You will be given specific instructions on insulin dosing and diet

for 3 days prior to the MMTT. On the morning of the test, your child may only drink water and will not take short acting insulin within 2 hours of the test. Your child will also be asked to not exercise 10 hours prior to this test as this can alter his/her blood sugar level. An IV cannula (plastic tube in vein) will be placed in his/her arm for drawing blood. Blood will be drawn from the IV cannula before drinking the Boost®. During the MMTT, no more than 5 tablespoons of blood will be drawn. Your child will be given 5 minutes to drink the Boost®, and then blood will be drawn up to 7 times for 2 hours. The amount of the drink will depend on your child's body weight but will be no more than 12 ounces.

- We will obtain from you the stool samples your child collected.
- We will download your CGM at this visit.

Early Discontinuation Visit:

Treatment will stop and we will ask that you will return for an exit visit if any of the following conditions occur:

- withdrawal of consent (we ask that you return for this exit visit, but you are not required to return)
- pregnancy (female participants)
- any medically important event such as a concurrent severe illness or complications
- it is in your best interest to stop the study in the investigator's judgment

You will have a visit at the hospital or research center, and it will last approximately 2-3 hours and will include:

- Measure your height and weight, check your vital signs, and examine you.
- We will ask you questions about your medical history, including your insulin use.
- Physical examination by the study doctor.
- For female adolescents: urine will be collected for a pregnancy test
- You will also be asked to fill out a diet history questionnaire or provide a diet diary (this can be done prior to the visit).
- You will be asked to provide a stool sample from the previous 3 days collected using the collection kit we provided you.
- Take blood samples (approximately 5 tablespoons total) to measure your blood sugar control and other things about your diabetes. This will include a MMTT if it has been 6 weeks since the last MMTT.
    - Some of the blood taken from you will be saved for the study doctors to use later. This is optional and you will be asked whether you agree to this at the end of this document.

RISKS OF TAKING PART IN THE STUDY:

While in the study, there may be side effects, risks, or discomforts. The most common and likely risks are described below; however, there may be some risks that are unknown. You/your child should discuss these with the study doctor. There is always the possibility that unknown or unexpected injuries might happen. There is a chance that your diabetes control may improve or worsen while you are involved in this study.

a. Blood Drawing and Urine Collection:

You/your child may have discomfort and/or a bruise when you get your blood drawn. Occasionally, some people may faint. It is rare, but some people may get an infection, a small blood clot, swelling of the vein and surrounding tissue, or bleeding at the needle puncture site. We will have trained medical professionals drawing blood to decrease these risks.

b. MMTT:

There are some risks with the MMTT. Use of Boost® during this test has no known side effects, but you/your child may not like the taste. Some people are allergic to soy or dairy products found in Boost®. If your child has any of these allergies, he/she will not be asked to participate. A hollow needle/plastic tube will be placed in your arm for taking blood samples during the MMTT. When the needle goes into a vein, it hurts for a short time. A special numbing cream may be used to make it hurt less. The most common risks related to putting the numbing cream (LMX or EMLA) on the skin are redness, blanching (temporary whiteness of the skin area), swelling, and itching. There may be minor discomfort from having the needle/plastic tube taped to your arm. There is a small risk of bleeding under the skin that will produce a bruise. There is a small risk of a blood clot forming in the vein, infection, or significant blood loss. We will have trained medical professionals inserting the IV to decrease these risks.

c. Risks of using the supplement:
The risks of this study include possible side effects of using the prebiotic supplement. Known risks of using the prebiotic supplement are derived from prior studies of the supplement in adults and children. Some of these are likely related to the intake of a relatively larger amount of fiber than typically consumed.

Likely: initial abdominal discomfort and increase in frequency of bowel movements

d. Potential risk for pregnancy: There is no evidence suggesting toxicity to fetuses with the supplement or placebo. Males participating in the study do not need to use contraceptive methods. Although generally considered to be safe, it has not been specifically studied in pregnant women and therefore, females of childbearing age will be asked to use the following:

Effective Forms of Birth Control – any one of the following (additionally, participants will be counselled on the use of a second method of contraception):

- Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
- Placement of an intrauterine device (IUD) or intrauterine system (IUS)
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

e. Risks related to CGM/sensor use:
The sensor may produce pain when it is inserted into the skin. There is a low risk for developing a local skin infection at the site of the sensor needle placement. Itchiness, redness, bleeding, and bruising at the insertion site may occur as well as local tape allergies.

f. Loss of Confidentiality:
There is the unlikely chance that health information is viewed by someone outside the research team who is not authorized to see health information. Efforts will be made to keep all personal information confidential. All data will be de-identified and stored with numerical identification and files will be kept in locked cabinets within locked rooms. Electronic data will be protected by 2 password systems (computer/database).

You may not experience any of these risks or you might have a problem we cannot predict. If we become aware of any new risks, you will be told about them, and can decide if you want your child to continue to participate in the study.

BENEFITS OF TAKING PART IN THE STUDY:

While receiving HAMS-AB, there are potential benefits in reduction of beta cell stress. We also hope to learn more about type 1 diabetes and whether the use of this supplement might improve glucose levels and/or improve beta cell health in general as well as restore the gut bacterial balance.

ALTERNATIVES TO TAKING PART IN THE STUDY:

Instead of being in this study, you can decide not to participate and receive standard treatment for your type 1 diabetes. This will not affect your medical care.

WILL I RECEIVE MY RESULTS?

We may learn things about you from the study activities which could be important to your health or to your treatment. If this happens, this information will be provided to you at the end of the entire study when all

participants are done. You may need to meet with professionals with expertise to help you learn more about your research results. The study team/study will not cover the costs of any follow-up consultations or actions.

CONFIDENTIALITY

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Your identity will be held in confidence in reports in which the study may be published.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the study investigator and his/her research associates, the Indiana University Institutional Review Board or its designees, the study sponsor (Indiana University School of Medicine) the Data Safety Monitoring Board, the Indiana Clinical Research Center, and (as allowed by law) state or federal agencies, specifically the Food and Drug Administration (FDA) and the National Institutes of Health (NIH), etc., who may need to access your medical and/or research records.

During your child's visits, as discussed above, blood samples will be collected. The blood and stool samples will be sent to a laboratory to be tested along with the blood and stool samples from all other patients in the study. The blood and stool samples will only be identified by the code number assigned to you/your child for the study.

Results of the study will be reported in medical journals and may be presented at scientific meetings. However, at no time will any of the participants in the study be identified. Confidentiality of your/your child's records will be maintained, and all records will be kept in accordance with current legal requirements.

A description of this clinical trial will be available on ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

For the protection of your privacy, this research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers may not disclose or use any information, documents, or specimens that could identify you in any civil, criminal, administrative, legislative, or other legal proceeding, unless you consent to it. Information, documents, or specimens protected by this Certificate may be disclosed to someone who is not connected with the research:

(1) if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases).
(2) if you consent to the disclosure, including for your medical treatment.
(3) if it is used for other scientific research in a way that is allowed by the federal regulations that protect research subjects.
(4) for the purpose of auditing or program evaluation by the government or funding agency.
(5) if required by the federal Food and Drug Administration (FDA).

A Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

USE OF INFORMATION FOR RESEARCH IN THE FUTURE

Information collected from you for this study may be used for future research studies or shared with other researchers for future research. If this happens, information which could identify you will be removed before any information is shared. Since identifying information will be removed, we will not ask for your additional consent.

COSTS

There is no cost to you for taking part in this study.

PAYMENT

Your child will receive payment for taking part in this study. Your child will get $50 in the form of a payment card for each completed visit, up to a maximum of $250 if you complete the entire study. In addition, parking will be paid for at each study visit. You will be reimbursed for mileage if your round trip is at least 30 miles roundtrip to the clinic at a rate of $0.17/mile.

COMPENSATION FOR INJURY

In the event of physical injury resulting from your participation in this research, necessary medical treatment will be provided to you and billed as part of your medical expenses. Costs not covered by your health care insurer will be your responsibility. Also, it is your responsibility to determine the extent of your health care coverage. There is no program in place for other monetary compensation for such injuries. However, you are not giving up any legal rights or benefits to which you are otherwise entitled.

CONTACTS FOR QUESTIONS OR PROBLEMS

For questions about the study or a research-related injury, contact the researcher Dr. Heba Ismail at 317-278-7041. If you cannot reach the researcher during regular business hours from 8:00 AM-5:00 PM, please call 317-944-3889.

In the event of an emergency, you may contact Dr. Ismail at 317-274-5000 and ask for her to be paged or the pediatric endocrinologist on call.

For questions about your rights as a research participant or to discuss problems, complaints, or concerns about a research study, or to obtain information, or offer input, contact the IU Human Subjects Office at (800) 696-2949 or irb@iu.edu.

VOLUNTARY NATURE OF STUDY

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. Your decision whether or not to participate in this study will not affect your current or future relations with Indiana University, Riley Hospital, or Pediatric Endocrinology.
Your participation may also be stopped by the study doctor for any reason without your consent. This may happen if you start taking an antibiotic or another medication that can affect your blood sugar or the balance and composition of the bacteria living in the intestine. If this were to happen, the study doctor may allow you to resume study participation once you are no longer taking the medication

STORED SAMPLES AND INFORMATION

If you agree, we will store your remaining samples and additional storage of serum and plasma at Indiana University. The purpose is to make these samples and information available for future research in diabetes or auto-immune disorders which is not yet planned. New scientific discoveries may lead to new tests. The tests may help researchers learn more about diabetes. These tests may include genetic testing. Genetic tests study an individual's inherited characteristics, found in DNA, which is present in each of the cells in your body. These tests may include whole genome sequencing, which involves mapping all your DNA.

This research follows the Genetic Information Nondiscrimination Act (GINA), a federal law which generally makes it illegal for health insurance companies, group health plans, and most employers to request the genetic information we get from this research and discriminate against you based on your genetic information.
Samples collected from you for this research may be used to develop products which could be sold in the future. The investigator does not plan to share any profits or losses from the sale of those products with you.

Your decision to allow samples and data to be stored is separate from your decision to participate in this study. If you decide to allow storage, your samples and data may be stored for an unknown length of time. No additional samples for storage are taken. Remaining samples are stored when all other study required tests are completed.

The results of tests done on your stored samples will not be given to you or your doctor. The results will not be put in your records and will not change your medical care. There will be no benefits to you from the storage of these samples and information. However, the use of your samples and information may help researchers learn more about diabetes or help study the genetics related to diabetes.

You can change your mind at any time during the study and ask to have your samples destroyed. This request should be made in writing to the study doctor or by phone to the study team. If your samples have not been used, they will be destroyed. If your samples have already been tested before your request, the information from these tests will be used and cannot be destroyed.

Choose yes or no to allow the storage of your remaining samples (blood and stool) and information for future tests.

Yes _____ (initials)

No _____ (initials)

SUBJECT'S CONSENT

In consideration of all of the above, I give my consent for my child to participate in this research study.
I will be given a copy of this informed consent document to keep for my records. I agree to take part in this study.

Subject's Printed Name: _____

Parent or Legal Guardian Printed Name: _____

Parent or Legal Guardian Signature: _____ Date: _____

Printed Name of Person Obtaining Consent: _____

Signature of Person Obtaining Consent: _____ Date: _____