COVER PAGE

Title: Understanding the Role of Gut Microbiota in Hyperphagia in Prader-Willi Syndrome

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CONSENT TO TAKE PART IN A RESEARCH STUDY

TITLE OF STUDY: Understanding the role of gut microbiota in hyperphagia
Principal Investigator: Keerthana Kesavarapu, DO

STUDY SUMMARY: This consent form is part of an informed consent process for a research study and it will provide information that will help you decide whether you want to take part in this study. It is your choice to take part or not.

The **purpose of the research** is to determine the effectiveness of using an Investigational New Drug NBT-NM108 to effect the bacteria in the intestines in patients who have Prader Wili Syndrome or hyperphagia and obesity from any reason. If you take part in the research, you will be asked to get a functional magnetic resonance imaging (fMRI, a scan of your brain), blood work, stool samples and to complete a questionnaire and 24-hour food recall. Once completed, you will be asked to eat a high fiber medication, NBT-NM108, once daily for 4 weeks. At the end of the 4-week period, you will repeat an fMRI, blood work, stool samples, questionnaire and 24-hour food recall.

Your **time in the study will take** 30 minutes for consent and eligibility interview; 1-hour for the initial testing including functional magnetic resonance imaging (fMRI) and blood draw; 10 minutes to take the medication ; 30 min for filling out a questionnaire and 24-hour food recall weekly; 10 min for collecting a stool sample weekly; 1-hour for end of study testing including functional magnetic resonance imaging (fMRI) and blood draw.

Possible harms or burdens of taking part in the study may be bruising or bleeding following blood draw tests, inconvenience for you and/or your family when you collect a stool sample at home, and abdominal discomfort and low blood sugar when you consume NBT-NM108. Lastly, fMRI can cause discomfort if you have issues with tight spaces or discomfort from loud noises and possible benefits of taking part may be reduced appetite or weight. You will not receive any direct benefit from taking part in this study

An **alternative to taking part in the research study**: Your alternative to taking part in the research study is not to take part in it.

The information in this consent form will provide more details about the research study and what will be asked of you if you choose to take part in it. If you have any questions now or during the study, if you choose to take part, you should feel free to ask them and should expect to be given answers you completely understand. After all your questions have been answered and you wish to take part in the research study, you will be asked to sign this consent form. You are not giving up any of your legal rights by agreeing to take part in this research or by signing this consent form.

Who is conducting this research study?
Keerthana Kesavarapu, DO is the Principal Investigator of this research study. A Principal Investigator has the overall responsibility for the conduct of the research. However, there are often other individuals who are part of the research team.

Keerthana Kesavarapu, DO may be reached at 732-235-7784, 125 Paterson St New Brunswsick, NJ 08901.

The principal investigator or another member of the study team will also be asked to sign this informed consent. You will be given a copy of the signed consent form to keep.

SPONSOR OF THE STUDY: Notitia Biotechnologies.

NAME OF DRUG/DEVICE MANUFACTURER: NBT-NM108/Safe Sterilization USA.

Why is this study being done?
Overeating leads to obesity and obesity related co-morbidities like diabetes that become one of the leading causes of death. There is, however, no effective treatment to decrease overeating. Our previous studies have shown that a high-fiber diet promotes a group of beneficial bacteria in the gut that is associated with improvements in body weight, blood sugar, and overeating. Dr Liping Zhao, PhD, who is a co-investigator on this study, has developed an Investigational New Drug (NBT-NM108) that provides a large amount of dietary fibers of different structures to support beneficial gut bacteria. In the current study, we will determine the effect of NBT-NM108 on changing the bacteria in our colons and how this affects eating behavior.

Who may take part in this study and who may not?
You may take part in this study if you meet the following criteria

- if you are between 18 and 45 years old.
- Genetically confirmed PWS or hyperphagia or obesity due to excess caloric intake
- Weigh less than 350lbs
- No growth hormone treatment in the previous 6 months
- Agree to practice contraception for 5 weeks or 7 days after the last dose of NBT-NM108 if you do not complete the 28-day intervention
- Have access to a smartphone, tablet, computer or other internet-enabled device and daily internet access, can understand and follow written and oral instructions in English
- Provide informed consent for participation.

Individuals who have treatments, conditions or diseases that are listed below may not take part in this study:

- History of active gastrointestinal disorders such as small intestinal bacterial overgrowth, celiac disease, inflammatory bowel disease or irritable bowel syndrome.
- Pregnancy or breastfeeding
- Self-reported allergy or intolerance to any ingredients in NBT-NM108
- Surgery involving the intestinal lumen within the last 30 days
- Immunocompromised, e.g., cancer treatment, bone marrow/organ transplant, immune deficiency, poorly controlled HIV/AIDS, prolonged use of steroids or other immunosuppressant medications
- Antibiotic administration in the previous 30 days.
- Growth hormone administration in the previous 6 months
- Individuals who are not proficient in English
- Contraindications for MRI scanning, including ferrous (iron) material implanted in or on the body, including flakes or filings, surgical clips, bullets, or electrical devices such as a pacemaker, or nonremovable ferrous jewelry (fillings in teeth and permanent retainers are permitted)
- Fillings and permanent retainers do not provide a safety risk and are not general exclusions. However, upper retainers may interfere with image quality and therefore are an exclusion
- Individuals with surgical pins or plates above the neck are excluded. Surgical pins or plates below the neck are exclusions, except when the material is fixed to bone, and considered acceptable.

Almost all recent orthopedic implants are made of materials that are not ferromagnetic and therefore are safe for scanning, and even though some screws are still made of ferromagnetic materials these are firmly screwed into bone. In cases where the material is unknown or deemed unsafe for scanning, the participant will be excluded.

- History of eye injury involving metallic materials, shavings in eyes, or welding without a face mask
- Lead/iron tattoos on the neck or face.
- History of significant anxiety in closed places
- Back problem that would prevent you from laying still comfortably for up to 90 minutes
- History of head trauma or neurosurgery. Current or past neurological disorder (other than headaches or peripheral nerve disease)

Why have I been asked to take part in this study?
You are invited to take part in this study because you meet some of the criteria for this study.

How long will the study take and how many subjects will take part?
We will recruit 13 participants to complete the entire study. For each participant it will take 4 weeks to complete the study. Overall, we expect to complete this study in 1 year.

What will I be asked to do if I take part in this study?
If you are being seen in our endocrinology clinic for hyperphagia or identified by the computer system, you will be called by our study coordinator to give an overview of the study, requirements for research participants, and review eligibility for the study. If you are interested in participating, you will be invited to the study center for consent and eligibility interview with our study coordinator via telemedicine. Then you will provide an electronic signature on the consent form to confirm that you agree to the eligibility screening process and give us permission to collect more information to decide whether you are suitable to take part based on our inclusion/exclusion criteria. If you are a female of child-bearing age (16-49 years), we may provide you with a pregnancy test kit to perform the test and confirm your pregnancy status with the research team to finalize enrollment.

After you are enrolled, you will be invited to the study site at Rutgers University, during which a functional magnetic resonance imaging (fMRI) will be performed before and after eating a meal. During the fMRI study you will be asked to lie still in the MRI scanner while pictures of the structure and activity in your brain are taken. During some of the time in the scanner, you will be asked to view pictures of food and other objects. You will be taken out of the scanner so you can eat, and then the scanning will be repeated. Additionally, blood work will be taken before and after (30, 60, 120, 180, and 240 minutes) eating the meal. You will be asked to complete a questionnaire and a 24-hour food recall. Lastly, you will be asked to provide a stool sample. Once the baseline testing is complete, you will be given NBT-NM108 to take daily for 4 weeks administered in the form of muffins. Hyperphagia questionnaire, 24-hour food recall and stool sample will be repeated weekly. Once the study is complete, you will be invited back to the study site at Rutgers University to repeat the fMRI, blood work, questionnaire, 24-hour food recall, and stool sample will be repeated.

If you are hospitalized during the study, you will be removed from the study and discontinue all data and sample collection.

What are the risks of harm or discomforts I might experience if I take part in this study?
Measuring blood tests during the study both involve a venous blood draw that pierces the skin. There may be a bruise, bleeding, or infection, at the place where the skin is pierced. However, infection is rare. Collecting stool samples at home may impose inconvenience for you and your family. You may experience

gastrointestinal symptoms (e.g. abdominal pain/discomfort, constipation or bloating) and low blood glucose when you take NBT-NM108. These discomforts are usually minor and generally last no longer than a few hours.

MRI Risks: There are no known health risks associated with the magnetic field produced by the scanner in healthy adults. Exposure to high magnetic fields is associated with primary or secondary risks in certain patient populations (e.g., patients with pacemakers), therefor such patients are excluded. Subjects with aneurysm clips, neural stimulators, possible metal fragments in the eyes, cochlear implants, artificial cardiac valves, iron based facial tattoos, and body piercings that are not removable are also excluded from participation. The only other risks associated with scanning are issues with tight spaces called claustrophobia while in the magnet, physical discomfort from lying still in the magnet, and the loud sound of the magnet. Screening interviews and the MRI screening questionnaire are used to rule out the presence of any medical or neurological problems that would cause a risk in the magnet.

The MRI exam could reveal an abnormality in your brain. This finding may be distressing to you. If there is any sign of an abnormality, the scan data is reviewed by a certified neuroradiologist through a contract with University Radiology Group (URG). The neuroradiologist provides a brief written evaluation that includes their recommendation as to whether any potential abnormality is clinically significant, and if it is, provides a recommendation for referral or further evaluation. Information about any observed abnormality will only be communicated with you if the neuroradiologist believes it requires further evaluation.

Are there any benefits to me if I choose to take part in this study?
The benefits of taking part in this study may be improvement on your eating habits and weight. However, it is possible that you may not receive any direct benefit from taking part in this study.

What are my alternatives if I do not want to take part in this study?
There are no alternative treatments available. Your alternative is not to take part in this study.

How will I know if new information is learned that may affect whether I am willing to stay in the study?
During the study, you will be updated about any new information that may affect whether you are willing to continue taking part in the study. If new information is learned that may affect you after the study or your follow-up is completed, you will be contacted.

Will I receive the results of the research?
In general, we will not give you any individual results from the study. If we find something of urgent medical importance to you, we will inform you, although we expect that this will be a very rare occurrence. You will receive a one-page summary of the overall findings of the study when the final data analysis is complete.

Will there be any cost to me to take part in this study?
There will be no cost to you.

Will I be paid to take part in this study?
You will receive up to $310.00 for taking part in this study. The compensation will be paid in the form of Clincards and amazon giftcards. The stipend will be available within one week after you successfully reach the following milestones:

- $25.00 after the completion of sample collection and shipment at Day 0

- $25.00 after the completion of sample collection and shipment at Day 28
- $30.00 after the completion of questionnaire and 24-hr diet recall at Day 0
- $30.00 after the completion of questionnaire and 24-hr diet recall at Day 28
- $50.00 after the completion of fMRI examination at Day 0
- $50.00 after the completion of fMRI examination at Day 28
- $50.00 after the completion of blood draw at Day 0
- $50.00 after the completion of blood draw at Day 28

If you do not complete the study, you will be compensated only for the part of the study that you have successfully completed. To receive payment, you must provide your social security number, name and address so that we can comply with IRS (Internal Revenue Service) reporting requirements. When payments are reported to the IRS, we do not tell them what the payment is for, only that you have been paid. If you do not wish to provide this information you can still take part in this study but you will not be paid.

Who might benefit financially from this research?

1. **University Holds Patent on a Product NBT-NM108:**
   Research studies like this one are designed to determine whether the product is safe and effective. Rutgers University owns a patent on some of the technology used in the product being studied. If research shows the product is safe and effective, Rutgers University would receive a part of the profits from any sales of the product.

2. **University Holds Equity in the Company Making a Product NBT-NM108:**
   This research is designed to test a product made by Notitia Biotechnologies. Rutgers University has an investment in Notitia Biotechnologies, such as stock. The financial value of this investment might be affected by the results of this study. This means that Rutgers University could gain or lose money depending on the results of this study.

3. **Investigator Is an Inventor/Could Receive Royalties on a Product NBT-NM108:**
   Research studies like this one are designed to determine whether the product (NBT-NM108) is safe and effective. Investigators Drs. Liping Zhao, PhD, Yan Lam, Guojun Wu and Cuiping Zhao, and research personnel Ms. Yongjia Gong are inventors of the product NBT-NM108 being studied. If research shows NBT-NM108 is safe and effective, Drs. Liping Zhao, PhD, Yan Lam, Guojun Wu and Cuiping Zhao and Ms. Yongjia Gong would receive a part of the profits from any sales of NBT-NM108.

4. **Investigator Holds Equity in the Company Making the Product NBT-NM108:**
   This research is designed to test a product made by Notitia Biotechnologies. Dr. Liping Zhao, PhD, one of the investigators on this study, has an investment in Notitia Biotechnologies, such as stock. The financial value of this investment might be affected by the results of this study. This means that Dr. Liping Zhao, PhD, could gain or lose money depending on the results of this study.

How will information about me be kept private or confidential?

All efforts will be made to keep your personal information in your research record confidential, but total confidentiality cannot be guaranteed. A code will be assigned to every participant and the collected data will be recorded using the participant's unique code for identification purposes. The Principal Investigators and research personnel who need to contact you will be the only one with access to the master code identifier. Participants' hard copy files will be kept in locked cabinets in a secured building. Electronic files

will be stored on All received health information will be stored in an encrypted password-protected file which is stored on the university's secure server and will only be accessible to authorized research personnel. The master code identifier and the data files will be kept in two separate locations. We will keep data in hard copies and the master code identifier for 6 years after study completion and then they will be permanently deleted from the server or shredded. Electronic data in de-identified form will be kept indefinitely. Imaging data is stored on a separate cloud-based server. Access to the data is controlled and only members of the research team have access to the data. Your name never appears with the imaging data. If team believes there is an abnormality on MRI that requires reading by a neuroradiologist, some of your imaging data will be sent to a server at University Radiology Group. No identifying information will be provided to University Radiology Group.

The research team may use or share your information collected or created for this study with the following people and institutions:

- The Rutgers University Institutional Review Board and Compliance Boards and its related staff who have oversight responsibilities for this study, and staff in Rutgers University Research Regulatory Affairs.
- The Office for Human Research Protections in the U.S. Dept. of Health and Human Services
- The Food and Drug Administration
- The research team, including the Principal Investigators, study coordinators, and all other research staff at Rutgers University
- Certain government and university people may need to know more about the study. For example, individuals who provide oversight on this study may need to look at your records. This is done to make sure that we are doing the study in the right way. They also need to make sure that we are protecting your rights and your safety.
- Any agency of the federal, state, or local government that regulates this research. This includes the Department of Health and Human Services (DHHS) and the Office for Human Research Protection (OHRP) and the Food and Drug Administration (FDA).
- Notitia Biotechnologies, and any persons or companies working for or with Notitia Biotechnologies.

A description of this clinical trial is available on http://www.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.

What will happen to my information—data, recordings and/or images—and biospecimens collected for this research after the study is over?

After information that could identify you has been removed, de-identified information and biospecimens collected for this research may be used by the investigator for other research without obtaining additional informed consent from you.

We may publish what we learn from this study. If we do, we will not include your name. We will not publish anything that would let people know who you are.

What will happen if I am injured during this study?

Subjects in this study may be exposed to certain risks of personal injury in addition to those associated with standard forms of treatment. In addition, it is possible that during the course of this study, new adverse effects that result in personal injury may be discovered.

If you get ill or are injured as the direct result of being in this study inform your study doctor, Dr. Keerthana Kesavarapu, DO 732-235-7784, as soon as possible. The Institution will make appropriate referrals for treatment. The Study Sponsor shall reimburse all the reasonable and necessary costs of diagnosis and treatment of any Study subject injury, including hospitalization, if it:

1. Is not a medical condition that you had before you started the study;

2. Is not the result of the natural progression of your disease or condition;

3. Is not caused by your failure to follow the study plan; and

4. Is not proved to be directly caused by the Institution's negligence or misconduct. There are no other plans for the University to provide other forms of compensation (such as lost wages) to you for research related illnesses or injuries. However, by signing this form, you are not giving up any legal rights to seek further compensation.

If you are not able to follow the study plan, please alert the investigator that you wish to withdraw from the study

What will happen if I do not wish to take part in the study or if I later decide not to stay in the study?
It is your choice whether to take part in the research. You may choose to take part, not to take part or you may change your mind and withdraw from the study at any time. If you do not want to enter the study or decide to stop taking part, your relationship with the study staff will not change, and you may do so without penalty and without loss of benefits to which you are otherwise entitled.

You may also withdraw your consent for the use of data already collected about you, but you must do this in writing to Dr. Keerthana Kesavarapu, DO (125 Paterson St, New Brunswick NJ 08901) or Dr. Liping Zhao, PhD (76 Lipman Dr, New Brunswick NJ 08901).

At any time, the study doctor can take you out of this study because it would not be in your best interest to stay in it. Your study doctor can stop treatment even if you are willing to stay in the study.

Who can I call if I have questions?
If you have questions, concerns or complaints about the research, wish more information, or if you feel you may have suffered a research related injury, you can contact:
Dr. Keerthana Kesavarapu, DO
Department of Gastroenterology
Rutgers- Robert Wood Johnson University
125 Paterson St, New Brunswick NJ 08901
Tel: 732-345-7784

Dr. Liping Zhao, PhD
Department of Biochemistry and Microbiology
School of Environmental and Biological Sciences
Rutgers University
76 Lipman Dr, New Brunswick NJ 08901

Department of Medicine
Division of Gastroenterology and Hepatology
Robert Wood Johnson Medical School
Rutgers, The State University of New Jersey
One Robert Wood Johnson Place, MEB 478
New Brunswick, NJ 08901

Tel: 848-932-5675

If you have questions, concerns, problems, information or input about the research or would like to know your rights as a research subject, you can contact the Rutgers IRB or the Rutgers Human Subjects Protection Program via phone at (973) 972-3608 or (732) 235-2866 or (732) 235-9806 OR via email irboffice@research.rutgers.edu, or you can write us at 335 George Street, Liberty Plaza Suite 3200, New Brunswick, NJ 08901.

PERMISSION (Authorization) TO USE OR SHARE HEALTH INFORMATION THAT IDENTIFIES YOU FOR A RESEARCH STUDY

The next few paragraphs tell you about how investigators want to use and share identifiable health information from your medical record in this research. Your information will only be used as described here or as allowed or required by law. If you sign this consent form, you agree to let the investigators use your identifiable health information in the research and share it with others as described below. Ask questions if there is something you do not understand.

What is the purpose of the research and how will my information be used?
You are being invited to take part in this research study which is described at the beginning of this form. The purpose of collecting and using your health information for this study is to help investigators answer the questions that are being asked in the research.

What information about me will be used?

- Your research record
- All of your past, current or future medical and other health records held by Rutgers University, other health care providers or any other site affiliated with this study as they relate to this research project. This may include, but is not limited to records related to HIV/AIDs, mental health, substance abuse, and/or genetic information
- Hospital discharge summaries
- Radiology records or images (MRI, CT, PET scans)
- Medical history or treatment
- Medications
- Consultations
- Laboratory/diagnostic tests or imaging
- EKG and/or EEG reports
- Pathology reports, specimen(s) or slide(s)
- Emergency Medicine reports

Who May Use, Share Or Receive My Information?
The research team may use or share your information collected or created for this study with the following people and institutions:

- Rutgers University Investigators Involved in The Study
- The Rutgers University Institutional Review Board and Compliance Boards

- The Office for Human Research Protections in the U.S. Dept. of Health and Human Services
- The medical staff that takes care of you and those who are part of this research study
- Any laboratories, pharmacies, or others who are part of the approved plan for this study
- The Data and Safety Monitoring Board or others who monitor the data and safety of the study
- The Food and Drug Administration
- Representatives of the Study Sponsor Notitia Biotechnologies
- Labs working with the Study Sponsor on this study
- Other authorized users

Those persons or organizations that receive the research subject's information may not be required by Federal privacy laws to protect it and may share your information with others without your permission, if permitted by the laws governing them.

Will I be able to review my research record while the research is ongoing?
No. We are not able to share information in the research records with you until the study is over. To ask for this information, please contact the Principal Investigator, the person in charge of this research study.

Do I have to give my permission?
No. You do not have to permit use of your information. But, if you do not give permission, you cannot take part in this study. (Saying no does not stop you from getting medical care or other benefits you are eligible for outside of this study.)

If I say yes now, can I change my mind and take away my permission later?
Yes. You may change your mind and not allow the continued use of your information (and to stop taking part in the study) at any time. If you take away permission, your information will no longer be used or shared in the study, but we will not be able to take back information that has already been used or shared with others. If you say yes now but change your mind later for use of your information in the research, you must write to the researcher and tell them of your decision: Dr. Keerthana Kesavarapu, DO (125 Paterson St, New Brunswick NJ 08901) or Dr. Liping Zhao, PhD (76 Lipman Dr, New Brunswick NJ 08901)

If you revoke your permission:

- You will no longer be a subject in this research study
- We will stop collecting new information about you
- We will use the information collected prior to the revocation of your authorization. This information may already have been used or shared with others, or we may need it to complete and protect the validity of the research
- Staff may need to follow-up with you if there is a medical reason to do so

How long will my permission last?
Your permission for the use and sharing of your health information will last the end of the research study.

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AGREEMENT TO TAKE PART IN RESEARCH

Subject Consent:

I have read this entire consent form, or it has been read to me, and I believe that I understand what has been discussed. All of my questions about this form and this study have been answered. I agree to take part in this study.

Subject Name (Print):_____

Subject Signature:_____Date:_____

Signature of Investigator/Individual Obtaining Consent:

To the best of my ability, I have explained and discussed all the important details about the study including all of the information contained in this consent form.

Investigator/Person Obtaining Consent (Print):_____

Signature:_____Date: _____