UNIVERSITY OF PENNSYLVANIA
RESEARCH SUBJECT INFORMED CONSENT FORM AND HIPAA AUTHORIZATION

Protocol Title: A Randomized, Double Blind, Placebo Controlled Study of the Effectiveness of Chronic Incretin-based therapy on Insulin Secretion in Cystic Fibrosis (Aim 2)

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Why am I being asked to volunteer?

You are being invited to participate in a research study on cystic fibrosis (CF) because you have been diagnosed with this disease. Your participation is voluntary which means you can choose whether or not you want to participate. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled. Before you can make your decision, you will need to know what the study is about, the possible risks and benefits of being in this study, and what you will have to do in this study. The research team is going to talk to you about the research study, and they will give you this consent form to read. You may also decide to discuss it with your family, friends, or family doctor. You may find some of the medical language difficult to understand. Please ask the study doctor and/or the research team about this form. If you decide to participate, you will be asked to sign this form.

What is the purpose of this research study?
In recent years, diabetes has emerged as one of the most significant co-diseases that many CF patients develop. Type 1 and Type 2 diabetes results when either the body does not make enough insulin or the body does not respond correctly to this insulin. Insulin is a hormone which is made by cells in the pancreas and helps carry glucose (sugar) from the food we eat to the cells of the body for energy. While cystic fibrosis related diabetes (CFRD) has many features similar to both Type 1 and Type 2 diabetes, it is very different; therefore, treatment and care of CFRD is not the same.

Relatively few patients with CFRD are identified by symptoms; therefore, annual screening with an oral glucose tolerance test is now recommended. We are inviting you to participate in this study because you have recently completed this routine oral glucose test or you have been diagnosed with CFRD.

- The purpose of this research study is to examine and understand the various mechanisms that contribute to CFRD and gain a better understanding of potential means to treat CFRD.

Who is funding this research study?
The study is being conducted with general research funds from National Institute for Diabetes, Digestive & Kidney Diseases.

How long will I be in the study? How many other people will be in the study?
Your participation in this study will include a screening visit and 6 study visits to the Clinical & Translational Research Center (CTRC) at the Hospital of The University of Pennsylvania (UPenn). You will have the option to stay overnight in the CTRC prior to some of your study visits which the study team will discuss with you further. Your participation in this study will be conducted over 6 months. Approximately 36 subjects, from various CF Centers, will participate in this research study. The entire study is expected to last approximately 4 years.

What am I being asked to do?

Screening Visit (early evening arrive in the CTRC)
- Medical history (review of your medical history, including the medications you currently use or have used in the last 45 days)
- Brief physical exam (including blood pressure, heart rate, breathing rate, weight and height measurements)
- Urine Pregnancy test for all females (the result of the pregnancy test must be negative for you to qualify to participate)
- Baseline safety laboratory tests (approximately 3 mL or ½ teaspoon)

If you qualify to participate, you can continue with the study procedures.
- Overnight fasting will begin at 8pm. You are allowed to have clear liquids until midnight and only water to drink after that.
- You may complete your overnight fast at home, if preferred, and return the next morning to the research center at approximately 7 am or you may opt to stay overnight at the CTRC.

Visit 1 (Baseline- Mixed Meal Tolerance Test):

Please do not take your routine morning ORAL medications before the study procedures. The study team will discuss this with you further.

This visit will take approximately 5 hours to complete. During the visit, the following will be performed:

- Measurement of your vital signs
- This will include blood pressure, heart rate, breathing rate and body weight.
- You will have a blood drawing IV placed. This will be utilized for the collection of blood samples throughout the visit to eliminate multiple sticks. The hand or arm with the blood drawing IV will be placed in a heated box or heating pad to keep warm in order to increase blood flow.

- Collection of blood samples (approximately 7 mL or 1½ teaspoons) for:
    1. HbA1c level-this is a useful indicator of how well the blood glucose level has been controlled in the recent past (last two to three months)
    2. Testing of the T7CF7L2 gene. Variations in this gene have been linkedwith diabetes although individual risk is currently unclear. This study will look at how common this gene occurs in patients with CF. There are no anticipated risks associated with this test.

- Mixed Meal Tolerance Test

This test will look at your body's response to food. Prior to this visit, you will work with the study team to decide on a breakfast that is appealing to you but is comprised of a specific combination of calories, protein and carbohydrates. You will take your routine pancreatic enzymes with this breakfast. After you eat, you will have blood drawn from your IV multiple times over a 4 hour period. The total amount of blood for this test is about 65mL or 4½ tablespoons.

- The next visit (Visit 2) can but does not have to be completed the following day. The study team will discuss this with you.

- Overnight fasting will begin at 8pm. You are allowed to have clear liquids until midnight and only water to drink after that.
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- You may complete your overnight fast at home, if preferred, and return the next morning to the research center at approximately 7 am.

Visit 2 (Baseline-Glucose Potentiated Arginine Test):

Please do not take your routine morning ORAL medications before the study procedures. The study team will discuss this with you further.

This visit will take approximately 5 hours to complete. During the visit, the following will be performed:

- You will be asked about any changes in your health. If your health or any medications have changed since your last study visit, you may be asked to come back at a different time or not to continue your participation.

- Measurement of your vital signs
  This will include blood pressure, heart rate, breathing rate and body weight.

- You will have two IV catheters placed
- One will be for blood drawing, to avoid multiple sticks; and the other is for an infusion of arginine (an amino acid) and glucose (sugar). The hand or arm with the blood drawing IV will be placed in a heated box or heating pad to keep warm in order to increase blood flow.

- Glucose Potentiated Arginine (GPA) test
- Arginine is a naturally occurring amino acid (substance) in your body. In this study it is given in your IV to make the cells in your pancreas secrete the hormone insulin. The GPA test will measure the insulin and other glucose controlling hormones which will assist in evaluating pancreatic endocrine function in response to injection of arginine at different levels of blood sugar.

- The study team will follow a schedule of administering arginine and checking your blood sugar levels over approximately an hour. After the first injection of arginine, you will receive a glucose infusion in order to raise the level of sugar in your blood (230 mg/dl). Once the level is achieved, arginine will be injected again, and then the glucose infusion will be turned off while your blood sugar and insulin levels return to normal.

- About 2 hours later, the glucose infusion and arginine injection will be repeated, this time at a higher level of sugar in your blood (340mg/dl). Once this level is reached, arginine will be injected a last time, and then the glucose infusion will be turned off. You will be allowed to eat lunch and your blood sugar will continue to be monitored over at least the next hour. You will be discharged once we confirm that your blood sugar level has normalized.

- The study team will monitor you closely during this testing, checking your blood sugar levels approximately every 5 minutes during the glucose infusions and every 10 – 30 minutes after they have stopped. The total amount of blood for this test is about 140mL or approximately 9 tablespoons.

- Randomization to study drug

At the end of your visit, you will be assigned by chance, like the flip of a coin, to get sitagliptin (Januvia ®) 100mg tablet or a matching placebo daily. The pill is to be taken every day for 6 months. Sitagliptin is a drug that helps the pancreas respond to insulin to lower your blood sugar levels after a meal. Neither you nor the study team will know whether you are taking sitagliptin or the placebo until you have completed the study.

- Blood sugar monitoring:

You will be given a little machine (called a glucometer) to measure your blood sugar every morning and evening. You will not have to pay for the glucometer or testing supplies at any time during the study. You will have to prick your finger and place a drop of blood onto a strip on the glucometer. You should check your blood sugar every day in the morning before breakfast and evening. *If your blood sugar is <70 mg/dL, then you must call the nurse practitioner whose number is listed on the front of this consent form.* ***Please bring your glucometer with you to each of your study visits. If you forget to bring your glucometer to your study visit we may ask you to call us and report your blood sugars when you get home.

Visit 3 at 1 month

Scheduled 1 month after starting your study medication (sitagliptin or placebo).

If you live out of the area, we will work with you to have this done locally.
*** Please bring all study medications to your visit.

- Collection of blood samples for clinical laboratory assessments
- Monitoring adherence

We will count the number of study pills remaining in your bottle. If the number or amount is higher than what we expect, a member of the research staff will call you weekly over the next month to remind you to take your study medication.

- We will review of your current medications and any illnesses or side effects from the study drug. Insulin dose adjustments will be made if you are on insulin and a review of any side effects.
- We will take your glucometer and download the information at your visit.

Phone call 1 at 2 months

We will contact you by phone during month 2 to ensure that you continue to do well on your study medication. This will also serve as a reminder to continue taking your study medication daily.

Visit 4 at 3 months

Scheduled 3 months after starting your study medication (sitagliptin or placebo)
If you live out of the area, we will work with you to have this done locally
.*** Please bring all study medications to your visit.

- Measurement of your vital signs

This will include blood pressure, heart rate, breathing rate and body weight (without shoes).

- Collection of blood samples for clinical laboratory assessments
- Monitoring adherence

We will count the number of study pills remaining in your bottle. If the number or amount is higher than what we expect, a member of the research staff will call you weekly over the next month to remind you to take your study medication.

- We will review of your current medications and any illnesses or side effects from the study drug. Insulin dose adjustments will be made if you are on insulin and a review of any side effects.
- We will take your glucometer and download the information at your visit.
- Pulmonary Function tests will be performed unless completed within 30 days of visit.

Phone calls 2 and 3 at 4 and 5 months

We will contact you by phone during months 4 and 5 to ensure that you continue to do well on your study medication. This will also serve as a reminder to continue taking your study medication daily.

Visit 5 at 6 months

Scheduled after completion of 6 months of blinded study medication (sitagliptin or placebo
*** Please bring all study medications to your visit.

Please do not take your routine morning ORAL medications before the study procedures. The study team will discuss this with you further.

This visit will take approximately 5 hours to complete. During the visit, the following will be performed:

- Measurement of your vital signs
  This will include blood pressure, heart rate, breathing rate and body weight and height.
- You will have a blood drawing IV placed. This will be utilized for the collection of blood samples throughout the visit to eliminate multiple sticks. The hand or arm with the blood drawing IV will be placed in a heated box or heating pad to keep warm in order to increase blood flow.
- Collection of blood samples (approximately 7 mL or 1½ teaspoons) for Mixed Meal Tolerance Test
- Overnight fasting will begin at 8pm. You are allowed to have clear liquids until midnight and only water to drink after that.
- You may complete your overnight fast at home, if preferred, and return the next morning to the research center at approximately 7 am.
- Mixed Meal tolerance test as described in Visit 1 above

Visit 6 at 6 months

Scheduled at the completion of 6 months of sitagliptin or placebo
Please do not take your routine morning ORAL medications before the study procedures. The study team will discuss this with you further.

This visit will take approximately 5 hours to complete. During the visit, the following will be performed:

- Measurement of your vital signs
  This will include blood pressure, heart rate, breathing rate and body weight.
- You will have two IV catheters placed
  One will be for blood drawing, to avoid multiple sticks; and the other is for an infusion of arginine (an amino acid) and glucose (sugar). The hand or arm with the blood drawing IV will be placed in a heated box or heating pad to keep warm in order to increase blood flow.
- Glucose Potentiated Arginine (GPA) test will be performed as described in Visit 2.

What are the possible risks or discomforts?

There are some potential risks and discomforts that may occur as part of the study. They are listed below. There may be other unforeseeable risks that are not mentioned here.

- Blood sample collections and IV catheter: The process for collecting blood samples requires a needle to be inserted into a vein. Possible side effects from blood drawing include faintness, inflammation of the vein, pain, bruising, or bleeding at the site of puncture. There is also a slight possibility of infection.
- Hypoglycemia/Fasting: Most people do not have medical problems associated with fasting; however, some people have medical conditions that limit their ability to tolerate a fast. If your doctor has told you not to fast, we ask that you not participate in this study. During this study, there is a small chance of having hypoglycemia (when your blood glucose is lower than normal). This has been reported in 1.2% of patients on sitagliptin therapy. If you have blood sugar < 70 mg/dL while on the study drug, please call the study team.
- GPA test: There is the possibility of experiencing a burning or stinging sensation as a result of the glucose infusion. Administration of arginine may briefly cause a metallic

taste in your mouth. Rarely, arginine may also cause nausea, vomiting, headache, flushing, numbness, allergy or rash, and irritation of the vein.

- Sitagliptin therapy: Rare cases (<1%) of pancreatitis which is severe abdominal pain with or without nausea have been reported with sitagliptin therapy. If you experience any abdominal pain that is persistant or radiating to your back while taking the study medication, please stop the medication and call the study team immediately. Hypersensitivity reactions have also been rarely reported with sitagliptin use. If you develop swelling of your lips, tongue, throat or face or skin rash please stop the study medication and call your study team immediately. Rarely, severe and disabling joint pain has been reported by patients treated with sitagliptin. If you develop any new or disabling joint pain, please stop the study medication and call your study team immediately. Their names and telephone numbers are located on page 1 of this consent form. Other common but less serious side effects including upper respiratory cold, diarrhea and nausea have been reported. Please call the study team if you have any of these symptoms. DNA-Genetic testing: There may be a risk that if people other than the study team have access to your genetic information they could misuse it. We think the chance of this ever happening to you is very small because your personal information will not be attached to the blood used for research. The laboratory personnel that will analyze your DNA will not know your personal information. The genetic results will be stored under a code number without any information that may identify you, in a secure, password-protected database. The investigators who view this database will not have access to your name or identifying information.
- If you are a woman that is pregnant, or plan to become pregnant, you will not be able to participate in this study. Pregnancy may alter the way your body handles sugar. If you are able to become pregnant you will be given a urine pregnancy test at the beginning of the study and at return visits. You will be asked to use a medically accepted method of birth control or the barrier method while you participate in this study. You should not become pregnant while you are participating in this study. If you do become pregnant, you must tell the study team at once to stop your participation in the study and consult an obstetrician or maternal-fetal specialist.

What if new information becomes available about the study?
During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

What are the possible benefits of the study?
You will not directly benefit from information learned as a result of your participation in this study. The knowledge gained from this study may help doctors better understand treatment of CF and glucose abnormalities. There is, however, no guarantee that you will benefit from your participation in this study.

What other choices do I have if I do not participate?
Participation in this study is optional. If you decide not to participate, your regular CF care will not be affected.

Will I be paid for being in this study?
You will be paid a total of up to $650.00 for your time and inconvenience related to your participation in this study. If you have extraordinary cost related to travel, the study will pay for these; you will know the details of this prior to coming to Philadelphia. If you do not complete the study, for any reason, you will be paid for the study visits you do complete according to the

following schedule: $150.00 for each MMTT and $150.00 for each GPA test visit and $25 each for Visits 3 and 4.
If you have any questions regarding your payment for participation, please contact the study doctor at the telephone number listed on page one of this consent form.

Please note that if you receive more than $600.00 compensation in one year for participation in research studies at the University of Pennsylvania, you must provide an Individual Tax Identification Number or Social Security Number for tax purposes. You will be asked to provide your Social Security Number for compensation that is provided in check form and/or is over $100.00. If you receive payment using a bankcard, the bank will have access to your name, address and phone number.

Will I have to pay for anything?
There will be no charge to you for your participation in this study. All study-related procedures, study visits and overnight stays will be provided at no charge to you or your insurance company.

What happens if I am injured from being in the study?
We will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them.

If you are injured as a result of the procedures done for the purpose of this study, there are no plans for The University of Pennsylvania or The Children's Hospital of Philadelphia to pay you or give you other compensation for the injury. You will not lose any of your legal rights or release the study doctor, the study staff, or study site from liability for mistakes or intentional misconduct by signing this consent form.

If you think you have been injured as a result of taking part in this research study, tell the person in charge of the research study as soon as possible. The investigators' names and phone numbers are listed on page one of the consent form. If you have an illness or injury during this research study that is not directly related to your participation in this study, you and /or your insurance will be responsible for the cost of the medical care of that illness or injury.

When is the Study over? Can I leave the Study before it ends?
Your participation in this study is voluntary. You may decide to not participate or you may leave the study at any time. Your decision will not result in any penalty or loss of benefits to which you are entitled.

The study doctors can stop your participation at any time without your consent for any reasons, including some of the following:

- If it appears to be medically harmful to you or in your best interest
- If you fail to follow directions for participating in the study
- If it is discovered that you do not meet the study requirements
- If the study is canceled
- If you become pregnant

What information about me may be collected, used or shared with others?
Information from your medical record will be used for this research project, including:

- Name, address, telephone number, date of birth, social security number (for payment purposes only)
- Diagnostic information regarding your CF diagnosis
- Chart review to ensure you meet the criteria for this research study (CF clinic visits, PFT results, laboratory results, etc.)

A description of this clinical trial will be available on http://www.clinicaltrials.gov, as required by 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.

Why is my information being used?
Your information is used by the research team to contact you during the study. Your information and results of test and procedures are used to:

- do the research
- oversee the research
- see if the research was done right

We are collecting multiple blood samples from each participant in the study. We need your medical record number so we know which blood tests come from the same patients. We will also use your medical record number to access your computerized medical records to complete your medical history.

Who can see or use my information? How will my personal information be protected?
We will do our best to make sure that the personal information obtained during the course of this research study will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. If this study is being overseen by the Food and Drug Administration (FDA), they may review our research records.

Who, outside the School of Medicine, might receive and share my information?
People and organizations that may inspect and/or copy your research records to conduct this research, assure the quality of the data and to analyze the data include:

- Members of the research team from The Children's Hospital of Philadelphia and The University of Pennsylvania
- Medical staff who are directly or indirectly involved in your care related to this research
- People who oversee or evaluate research and care activities at CHOP and UPenn
- People from agencies and organizations that perform independent accreditation and oversight of research
- The makers of the study medication, Merck Sharpe & Dohme Corp, may receive your information in the case of any illness or injury that may be related to the study medication.

Once your personal health information is disclosed to others outside the UPenn School of Medicine, it may no longer be covered by federal privacy protection regulations. The Principal Investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to University of Pennsylvania procedures developed to protect your privacy.

How will my personal information be protected?
You will be assigned a number for the research study; this number will be linked to your medical record number at the University of Pennsylvania or The Children's Hospital of Philadelphia. The

file connecting your research number to your medical record number will be maintained in a locked file accessible only to members of the research team.
Results of the blood tests will not be entered into your medical record. Your name and other personal information will be removed from any test results before they are published, presented at scientific meetings, or discussed with anyone outside of the research team. We will do our best to make sure that the personal information in your medical record will be kept private.

How long may the School of Medicine use or disclose my personal health information?
Your authorization for use of your personal health information for this specific study does not expire.

Your information may be held in a research database. However, the UPenn School of Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization
- The University of Pennsylvania's Institutional Review Board grants permission
- As permitted by law

Can I change my mind about giving permission for use of my information?
Yes. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the investigator for the study. If you withdraw your permission, you will not be able to stay in this study.

What if I decide not to give permission to use and give out my health information?
Then you will not be able to be in this research study.
You will be given a copy of this Research Subject HIPAA Authorization describing your confidentiality and privacy rights for this study.
By signing this document you are permitting the UPenn School of Medicine to use and disclose personal health information collected about you for research purposes as described above.

Electronic Medical Records and Research Results
What is an Electronic Medical Record?
An Electronic Medical Record (EMR) is an electronic version of the record of your care within a health system. An EMR is simply a computerized version of a paper medical record.

If you are receiving care or have received care within the University of Pennsylvania Health System (UPHS) (outpatient or inpatient) and are participating in a University of Pennsylvania research study, results of research-related procedures (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in your existing EMR maintained by UPHS.

If you have never received care within UPHS and are participating in a University of Pennsylvania research study that uses UPHS services, an EMR will be created for you for the purpose of maintaining any results of procedures performed as part of this research study. The creation of this EMR is required for your participation in this study. In order to create your EMR, the study team will need to obtain basic information about you that would be similar to the information you would provide the first time you visit a hospital or medical facility (i.e. your name, the name of your primary doctor, the type of insurance you have). Results of research procedures performed as part of your participation in the study (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in this EMR.

Once placed in your EMR, these results are accessible to appropriate UPHS workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by UPHS to be appropriate to have access to your EMR (e.g. health insurance company, disability provider, etc).

Who can I call with questions, complaints or if I'm concerned about my rights as a research subject?

If you have questions, concerns or complaints regarding your participation in this research study or if you have any questions about your rights as a research subject, you should speak with one of the Principal Investigators listed on page one of this form. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the Office of Regulatory Affairs with any question, concerns or complaints at the University of Pennsylvania by calling (215) 898-2614.

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania to disclose that personal health information to outside organizations or people involved with the operations of this study.

A copy of this consent form will be given to you.

Optional Consent for Specimen Bank

In addition to the activities described in the full consent form, you are being asked to give permission for your extra blood specimens to be saved for an indefinite period (this is called Specimen Banking). These specimens will only be used for future research about cystic fibrosis.

Please read each statement below and initial and date the line next to your choice.

_____ YES, I give permission for banking of my extra blood specimens.

_____ NO, I do not give permission for banking of my extra blood specimens.

Consent to Participate in this Research Study

Name of Subject (Please Print)	Signature of Subject	Date

Name of Person Obtaining Consent (Please Print)	Signature	Date