Title of research study: Phase I Study to Determine the Optimal Human Challenge Dose for Norovirus GII.4CIN-3 Batch No.: 01-16C3

DMID 17-0102

Key Information:

The following is a short summary of this study to help you decide whether to be a participant in it. More detailed information about the study is listed later in this form. This document does not replace the discussion you should have with the research team about this study including having any questions or concerns answered.

You and about 100 other people about your age are being asked to screen to be in this research study. About 48 people will participate in the overnight portion of the study. The study is being done so we can learn more about how much norovirus it takes to cause an infection. This knowledge will allow us in the future to test products to prevent and/or treat norovirus. You will be in this study for about 6 months.

This is a consent form. It explains this research study. If you decide that you want to be in this research study, then you will sign this form to show that you agree to be part of this study. If you sign this form, you will receive a signed copy of it for your records.

Investigator: Robert Frenck, MD

Contact Info:
Gamble Program for Clinical Studies
513-636-7699

Industry Protocol #:
DMID 17-0102

Test Article Name:
Norovirus GII.4/CIN-3 Challenge

Funding: National Institutes of Health

Reason for the study:

The main reason for this research study is to learn more about the safety of giving people a norovirus infection and how much norovirus it takes to cause an infection. We want to learn more about norovirus infections and how your body responds after being infected by the virus.

Noroviruses are one of the most common causes of diarrhea in the world. Symptoms of norovirus, which usually last 2 to 3 days, may include diarrhea, vomiting, nausea, abdominal cramps, pain and gurgling, headache, fever, muscle aches, and fatigue. Norovirus can spread easily and quickly often resulting in large outbreaks. Currently, there is no vaccine and no medicines that make norovirus infections better. In young children and elderly people, norovirus infection can cause severe illness.

Noroviruses cannot be grown in the laboratory or in animals; so we can only study drugs or vaccines for the norovirus in humans. For this study, you will be given a dose of norovirus that has been taken from the stool of someone who was previously sick with norovirus infection. This stool was purified and then filtered. After the stool was filtered, it was tested for other infections. The only

infection found was norovirus. While we did not find any other infections in the stool, we cannot be absolutely certain there are no other infections. Extensive testing has been done on the person who donated the norovirus stool sample to make sure he/she did not have any other infections other than norovirus at the time of donation.

Initially you will be screened for study eligibility. If after screening you remain eligible, you will be admitted to our inpatient research unit for 5 days. On the day after admission to the inpatient unit, you will be given a dose of the challenge virus to drink in a cup of water. Then, for the next 4 days you will be watched closely to see if you become ill. If you become ill, you will be cared for by our study staff and study doctors at no cost to you. **You will not be able to leave nor have visitors while you are in the overnight unit.**

You **cannot** be in the study if:

- You live with or have daily contact with anyone who is younger than 2 years of age or older than 70 years of age or anyone who has trouble fighting infections or has had cancer, a transplant or HIV
- You will live or stay in a dormitory, a camp, a ship or other confined space
- You are a healthcare worker or are in food service
- You are a woman who is pregnant or breastfeeding
- You test positive for opiates in your urine drug screen, have Hepatitis B, C, or HIV or other problems fighting infection
- You have recently had norovirus infection or have ever had a norovirus vaccine
- You are in any other interventional research studies right now
- You are positive for COVID-19 by a rapid antigen test at the time of admission to the challenge unit

There may be other reasons you would not qualify to do this study. Study staff will review these with you.

Females must be abstinent (not currently having sexual intercourse that may result in pregnancy) or must be using an acceptable form of birth control for at least 30 days prior to study enrollment and continue through 45 days after receipt of challenge dose. Females who are capable of bearing children must have negative pregnancy testing to take part in the study. Study staff will talk with you more about the birth control methods. There may be other reasons you cannot be in this study, and the study staff will review these with you.

The research staff will explain each visit to you and may give you a handout that explains each visit in more detail. You will be able to ask questions to make sure that you understand what will happen.

Procedures:

WHAT WILL HAPPEN IN THE STUDY?

Study Visits

SCREENING

Screening for this study can take place over a period of up to 2 months. You will be asked to come to the clinic for 1 or more screening visits to see if you qualify to be in this study. Screening visits may take up to 2 hours. If you qualify for the inpatient part of the study and do not get admitted or you are an alternate for a study group and are not challenged, you may be asked to re-screen for a different study group. If you re-screen for a different study group you will start the screening process again from the beginning.

The research staff will explain the study to you and give you a handout that explains what will happen at each study visit. You will be able to ask questions to make sure that you understand what will happen.

OVERNIGHT UNIT

On arrival to the overnight unit the study team will:

1. Ensure continued eligibility
2. Administer a written test for study comprehension that you will need to pass
3. Obtain a nasal swab for COVID-19 antigen testing. If you are found to be positive for COVID-19, you will be immediately escorted out of the challenge unit and will not be administered the dose of norovirus.

If you, pass the study comprehension exam and are negative on the COVID-19 antigen test, you will be admitted to our overnight unit. The day following admission, you will receive a dose of norovirus germs. You will not be able to eat or drink anything for 90 minutes before and after receiving the norovirus germs. The study staff will explain this in further detail at your visit.

You will stay at least 4 more days after challenge and go home when you no longer have illness symptoms and are feeling better. If, due to a personal emergency, you need to leave the overnight unit before 4 days, you will be given information about how to prevent the spread of norovirus infection, asked to be seen by a study investigator to review any symptoms or problems, have any scheduled study labs collected, and you will be asked to return to the next outpatient visit. If you decide to leave the overnight unit early, you will be compensated for the portion(s) of the study you completed.

For about a week after your stay on the overnight unit, you will be asked to enter into an online database your temperature and how you are feeling. For about a month after going home from the inpatient unit you will be asked to report medicines you take, changes in your health, and medical or emergency room

visits. You will be asked to come back to the outpatient clinic for at least 5 visits. You will bring in a stool sample to these visits. At about 6 months, we will contact you to make sure you are okay.

We will have several alternates for this study. You will know ahead of time if you are an alternate. If you are an alternate, you will be admitted to the overnight unit and complete the study procedures, however, you may be sent home after one night and you will be compensated for your time.

Risks to Participate:

The bad things that can happen from blood draws are pain or bruising where the needle goes into the vein or feeling faint when the blood is drawn. Although it is rare, it is possible to develop a blood clot in the vein you have your blood collected from and some people have gotten an infection from having their blood drawn. Trained staff collecting samples will clean your skin properly and apply pressure at the site after the blood draw is complete.
To minimize some of these risks, trained staff collecting samples will clean your skin properly and apply pressure at the site after the blood draw is complete.

COMMON RISKS OF BLOOD DRAWS, SOME MAY BE SERIOUS
• Pain • Bruising where blood is collected from • Feeling light-headed or fainting • Blood clot in the vein you have your blood collected from • Infection where blood was collected from

The norovirus germs used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood, causing side effects. The table below shows the most common and most serious side effects that researchers know about. We do not know all of the side effects that may occur.

COMMON RISKS OF NOROVIRUS INFECTION, SOME MAY BE SERIOUS
• Diarrhea • Feeling feverish (or maybe having an actual fever) • Fatigue (feeling tired) • Chills • Skin irritation from diarrhea • Nausea and/or vomiting • Stomach pain, cramping, gurgling or gas • Anorexia (loss of appetite)

- Headache
- Body aches

You probably won't get severe vomiting or diarrhea but if you do, it may cause you to become dehydrated. If you are dehydrated we will give you lots of fluid to drink and we may give you fluid through a vein in your arm or hand. There will be medicines available to treat any skin irritations.

Not eating for 90 minutes before and after receiving the challenge virus could cause dizziness, headaches, stomach ache or fainting.

There is a slight chance you may be exposed to other infections from the norovirus. You may not be able to donate blood while you are in this study. There may be other risks that are unknown at this time.

You should not be in this study if you are pregnant. Because there may be risks to you or your baby that we do not yet know about, women should not become pregnant the entire time they are in the study. You should notify your study staff immediately if there is a pregnancy.

Acquisition/Spread of COVID-19
The COVID-19 pandemic is ongoing. It is possible that you could catch COVID-19 from other study participants. To minimize this risk, all participants will have a negative rapid test for COVID-19 at the time of admission to the inpatient unit. Any participant found to have a positive COVID-19 test will be escorted out of the inpatient unit and they will not be administered a dose of norovirus.

Benefits to Participate:

There is no benefit to you for being in this study. When we finish the study, we hope that we will know more about norovirus infections. This may help other people with norovirus infections later on.

Other Options:

Participation in research is completely voluntary. Your decision to participate or not to participate will not affect the care you receive. Instead of being in this study you can choose not to be in this study.

If you want to stop being in the research study, all you have to do is tell Dr. Frenck or someone else on the study staff.
If you decide not to be in the study, you will still receive good care.

If you decide you do not want to participate or if you withdraw from the study, it will not affect your job or employment in any way. If you decide to end the study early, you will not be given any further study product. You may be asked to provide urine, blood, stool, or saliva samples and asked to be followed for safety.

Cost to Participate:

The study doctor will tell you if they find out about new information from this or other studies that may affect whether or not you want to stay in this study.
It will not cost you anything to be in this study. The lab tests, study visits and other study tests will be provided at no charge to you or your insurance company.

There will be no additional costs to you for being in this study.

Payment:

If you agree to take part in this research study, we will pay you for the portion(s) of the study that you complete.

If you do not pass the initial screening visit you will be paid $20. If you successfully pass the initial screening you will be paid $50 for that visit. Any additional visits completed during the screening period will be reimbursed at $50 for each visit.

You also will be compensated for the overnight portion of the study as well as post-challenge visits. The details of these payment are listed in a handout you will be given.

You will receive payment for this study in the form of a reloadable debit card (Clincard). We will give you a handout that will explain how to use the card. Because you are being paid for your participation, Cincinnati Children's is required by the Internal Revenue Service (IRS) to collect and use your social security number (SSN) or taxpayer identification number (TIN) to track the amount of money that we pay. You will need to complete a Federal W-9 form for this income tax reporting. This form requires your Social Security number. This form will be given to the Cincinnati Children's business office. It will not be kept as part of your study chart. If you move, you will need to complete another W-9 with an updated address.

Tissues or body fluids collected for this research (de-identified) may be used to create products, including some that could be patented/licensed and sold. If this happens, there are no plans to tell you, or to pay you, or to give any compensation to you or your family.

Additional Study Information:

The following is more detailed information about this study in addition to the Key Information.

If I have Questions or would like to know about:

Who to talk to…	**You can call …**	**At …**
• Emergencies • General study questions • Research-related injuries • Any research concerns or complaints	**Dr. Frenck**	Phone: 513-803-5085
• Emergencies • General study questions • Research-related injuries • Any research concerns or complaints	**Susan Parker**	Phone: 513-636-7699
• Your rights as a research participant	**Institutional Review Board** This is a group of scientists and community members who make sure research meets legal and ethical standards.	Phone: (513) 636-8039

Total number of participants:

We expect about 100 people will undergo screening and about 48 will be asked to be part of the challenge phase of the protocol.

Detailed Procedures:

SCREENING:

- We will measure your body weight and check your blood pressure, heart rate, and temperature
- We will ask you about any past or present illnesses and medicines you take
- We will test your saliva (spit) to see if you are susceptible to norovirus
- If you are female, we will test you to see if you are pregnant
- The study doctor or nurse practitioner will perform a brief physical exam
- We will take blood, urine, saliva and stool samples from you to see if you qualify to be in the study, including whether or not you already have protection to norovirus, and to make sure you are healthy, including drug screening for opiates and testing for HIV, Hepatitis B and C, kidney and liver function, blood cell count
- You will be given education materials and a written test to make sure you understand what the study is about and what you will be asked to do if you

take part in this study

OVERNIGHT UNIT

- **Medical history** – we will ask you questions about any past or present illnesses, hospitalizations, surgeries, and medications you take.
- **Physical exam** – we will measure your weight on admission and may also check it at other times during illness to make sure your weight is not dropping off. We will check your blood pressure, temperature, and heart rate daily and may check them more often if you are ill. A study doctor or nurse practitioner may do a brief physical exam each day you are in the overnight unit to make sure you are healthy.
- **Blood, urine, saliva, and stool sample collection** – we will take blood, urine, saliva and stool samples from you to make sure you qualify to be in this study, are healthy, and to see how you are responding to the norovirus. We will also take blood, urine, and stool samples to monitor your well-being and safety throughout the whole study. The amount of blood taken from you while in the study is outlined in the norovirus handout. When you are in the overnight unit, we will give you containers to collect all your stools and vomit.
- **Norovirus** - You will be admitted to the inpatient unit the day before you receive the challenge dose. On the day of challenge you will receive a dose of norovirus germs after you have spent one night on the unit. You will not be able to eat or drink anything for 90 minutes before and after receiving the norovirus germs. The study staff will explain this in further detail at your visit.

You will be given a study handout separate from the consent that shows when visits are planned, what will happen at each visit, and what you will be paid for each completed visit.

The study doctor may decide to take you off this study at any time if it is in the best interest of your health or the study is ended early for any reason.

Your participation in this study may be stopped by the study doctor or study sponsor without your permission.

Change of Mind/Study Withdrawal:

You can leave the research at any time; it will not be held against you.

The person in charge of the research study or the sponsor can remove you from the research study without your approval if the study doctor believe it is in your best medical interest.

If you stop being in the research, data already collected may not be removed from the study database. You will be asked whether the investigator can collect data from your routine medical care.

We will tell you about any new information that may affect your health, welfare, or choice to stay in the research.

We do not know all of the risks to an unborn baby if you do this study. You should not be in this study if you are breast-feeding, pregnant, or planning to become pregnant during the time you are in this study.

Privacy:

You will be registered in the Cincinnati Children's Hospital Medical Center's computer system as a research subject. A copy of this consent form will be included in your research chart. To keep your information private and confidential, Cincinnati Children's Hospital Medical Center and/or the study doctor will:

- Use code numbers instead of your name in your study chart
- Limit the people who can see your study records
- Not identify you in any records or articles published about the study findings

By signing this consent form you are giving permission for parts of your medical and research records related to this study to be reviewed by:

- Cincinnati Children's Hospital Medical Center (CCHMC)
- The study doctor and CCHMC research staff who are part of the study
- The CCHMC Institutional Review Board and the Office for Research Compliance and Regulatory Affairs
- The sponsoring company or designee
- Your personal health care provider
- Study monitors and medical monitors contracted by the study sponsor

Efforts will be made to limit the use and disclosure of your personal information, including research study and medical records, to people who have a need to review this information. We cannot promise complete privacy. Organizations that may inspect and copy your information include the IRB and other representatives of this organization.

The Food and Drug Administration (FDA) may choose to inspect your records because you are a participant in this study and they are in charge of studies of experimental, unapproved test articles, including the norovirus challenge being used in this study.

To help us protect your privacy, we have a Certificate of Confidentiality from the National Institutes of Health (NIH). The researchers can use this Certificate to legally refuse to give information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify

you, except for reporting of communicable diseases to State and local health departments.

The Certificate of Confidentiality:

- Will not be used to prevent disclosure to state or local authorities for information required by local or state law.
- Cannot be used for information in your medical records.
- Does not prevent disclosure of your information to the NIH, Food and Drug Administration (FDA), or federal funding agency.
- Does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research.

If you give your consent to release information to a medical care provider, an insurer, or other person to receive research information, then the researchers will not withhold that information.

Samples and/or data collected for or generated from this study could be shared and used for future research. Samples and /or data may be shared with other collaborators at Cincinnati Children's and possibly with outside collaborators, who may be at another institution or for-profit company.

If information that could identify you is removed from your information or samples collected during this research, that information or those samples could be stored and used for future research studies or distributed to another investigator for future research studies without your additional informed consent.

The sponsor, monitors, auditors, the IRB, the Food and Drug Administration will be granted direct access to your medical records to conduct and oversee the research. By signing this document, you are authorizing this access. We may publish the results of this research. However, we will keep your name and other identifying information confidential.

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

If injured while in the study:

Dr. Robert Frenck, M.D., is the study doctor in charge of this study at Cincinnati Children's Hospital Medical Center.

If you believe that you have been injured as a result of this research, you should contact Dr. Frenck as soon as possible to discuss the concerns. Treatment for

injuries is available at Cincinnati Children's. If you go to the Emergency Room or to another hospital or doctor, it is important that you tell them that you are in a research study. If possible, you should give them a copy of this consent form. Cincinnati Children's follows a policy of making all decisions about compensation for the medical treatment of physical injuries that happened during or were caused by research on an individual basis.

In general, no long-term medical care or financial compensation for research-related injuries will be provided by the NIH or the Federal Government.

Return of results:

Most tests done on samples or images obtained in research studies are only for research and have no clear meaning for healthcare. If the research with your information or samples gives results that do have meaning for your health, the researchers will contact you and ask you if you would like to know what they have found. You can say No to hearing about the results at that time if you desire.

AUTHORIZATION FOR USE/DISCLOSURE OF HEALTH INFORMATION FOR RESEARCH

To be in this research study you must also give your permission (or authorization) to use and disclose (or share) your "protected health information" (called PHI for short).

What protected health information will be used and shared during this study?

Cincinnati Children's Hospital Medical Center (Cincinnati Children's) will need to use and share your PHI as part of this study. This PHI will come from:

- Your Cincinnati Children's medical records
- Your research records

The types of information that will be used and shared from these records include:

- Laboratory test results, diagnosis, and medications
- Reports and notes from clinical and research observations
- Imaging (like CT scans, MRI scans, x-rays, etc.) studies and reports
- If applicable, information concerning HIV testing or the treatment of AIDS or AIDS-related conditions, drug or alcohol abuse, drug-related conditions, alcoholism, and/or psychiatric/psychological conditions (but not psychotherapy notes).

Who will share, receive and/or use your protected health information in this study?

- Staff at all the research study sites (including Cincinnati Children's)
- Personnel who provide services to you as part of this study
- Other individuals and organizations that need to use your PHI in connection with the research, including people at the sponsor and organizations that the sponsor may use to oversee or conduct the study.
- The members of the Cincinnati Children's Institutional Review Board and staff of the Office of Research Compliance and Regulatory Affairs.

How will you know that your PHI is not misused?

People that receive your PHI as part of the research are generally limited in how they can use your PHI. In addition, most people who receive your PHI are also required by federal privacy laws to protect your PHI. However, some people that may receive your PHI may not be required to protect it and may share the information with others without your permission, if permitted by the laws that apply to them.

Can you change your mind?

You may choose to withdraw your permission at any time. A withdrawal of your permission to use and share your PHI would also include a withdrawal from participation in the research study. If you wish to withdraw your permission to use and share PHI you need to notify the study doctor, listed on the first page of this document, in writing. Your request will be effective immediately and no new PHI about you will be used or shared. The only exceptions are (1) any use or sharing of PHI that has already occurred or was in process prior to you withdrawing your permission and (2) any use or sharing that is needed to maintain the integrity of the research.

Will this permission expire?

Your permission will expire at the end of the study.

Will your other medical care be impacted?

By signing this document, you agree to participate in this research study and give permission to Cincinnati Children's to use and share your PHI for the purpose of this research study. If you refuse to sign this document you will not be able to participate in the study. However, your rights concerning treatment not related to this study, payment for services, enrollment in a health plan or eligibility of benefits will not be affected.

FUTURE CONTACT

We may want to contact you in the future to see if you would be interested in participating in future studies. If and when you are contacted, you can decide if you want to participate in any of the other studies and will sign another consent form to participate in those studies.

Please initial whether or not you give your permission to be contacted regarding future studies:

_____ **YES, I may** be contacted about future studies.
Initials

_____ **NO, I may not** be contacted about future studies.
Initials

FUTURE USE OF SPECIMENS

All remaining samples collected from study participants (ie. blood, saliva, and stool) will be kept for an indefinite amount of time after the study is completed. Your name and identifying information will be removed from these leftover study specimens.

It is possible that these stored samples might be useful for future research. These samples might be used in new or different laboratory tests, to provide information for the development of new vaccines, or for the studies of norovirus or other infections. The samples might be shared with researchers at other study centers. There are no benefits to you in the collection, storage and future research use of these blood samples. The results of any future testing will be kept confidential.

SIGNATURES

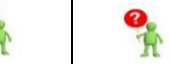
The research team has discussed this study with you and answered all of your questions. Like any research, the researchers cannot predict exactly what will happen. Once you have had enough time to consider whether you should participate in this research, you will document your permission by signature below.

You will receive a copy of this signed document for your records.

_____
Printed Name of Research Participant

_____ _____

Signature of Individual Obtaining Consent Date

Study Period	Outpatient Screening	Inpatient Challenge Admission		Outpatient Follow Up					Final Study Contact
Procedure	**Day -60 to Day -2**	**Day -1 Admission**	**Inpatient Admission Day 1-5***	**Day 6**	**Day 15**	**Day 30**	**Day 45**	**Day 60**	**Day 180**
Consent/Review Eligibility Criteria	✓	✓	✓						
Safety Questions					Diary 				
Study Education/Materials	✓								
Written Test of Understanding (may be given at one of the visits indicated)	✓	✓	✓						
Vital Signs (temperature, pulse, blood pressure will be measured at screening and other visits, based on illness symptoms))									
Physical Exam									
Brief Physical Exam (if needed, based on illness symptoms)									
Urine Pregnancy Test (childbearing females will have pregnancy testing at screening and on admission to the inpatient unit, prior to challenge)									

Nasal Swabbing for COVID (must test negative to continue with study admission)									
Blood Tests			**Day 2,4,5**						
Stool Sample Testing If you are not able to produce a stool, you may be asked to use a rectal swab to collect the sample									
Urine Test for health and opiates									
Challenge (Norovirus germs given in a cup of water)			**Day 1**						
Given Memory Aids to complete and return at study visit(s).			5-day Memory Aid for illness						
Bring Memory Aid to Review at study visit									
Planned Discharge			**Day 5**						
Clincard Upload	**$50 screen** **$20 screen fail**	**$350 overnight/ alternate**	**$350 each overnight**	**$100**	**$100 +$25 Diary Completion**	**$100**	**$100**	**$100**	**$50 final study contact** **$125 all visits completed#**

What Will Happen In The Study

How Will I Be Reimbursed for Participating?

We will give you your payment in the form of a reloadable debit card (ClinCard) and you will receive a handout that will explain how to use the card. We will provide you with a card and we will load money onto your card after each visit that you complete based on the schedule listed below.

- $50 at each screening visit
  - If you come in for a screening study visit and are **not eligible** that day, you will receive $20
- $350 each overnight
  - If you have to stay an extra night, you will receive an additional $350 (you may be asked to stay longer if you have illness symptoms)
  - If you are an **alternate** on the overnight unit you will receive $350
- $100 for scheduled clinic visits
- $50 if you are asked to come in for an unscheduled visit

- $50 for completing final study contact
- $125[#] final study contact to study participants who complete **all scheduled study visits**.
- If you are unable to complete the study, you will be paid for each study visit that you do complete
- $25 for Diary Completed

This research study involves payment for participation. We are required by Internal Revenue Service (IRS) rules to collect and use your social security number (SSN) or taxpayer identification number (TIN) in order to track the amount of money that we pay you. Unless you have given specific permission for another use of your SSN or TIN related to this research study, we will only use your SSN or TIN to keep track of how much money we pay you and your SSN or TIN will not be used as part of this research study.