UNIVERSITY OF MICHIGAN

CONSENT TO BE PART OF A RESEARCH STUDY

1. KEY INFORMATION ABOUT THE RESEARCHERS AND THIS STUDY

Sub-study title:

Direct Measurement of GI Permeability Change in Response to Aquamin®

Main study title:

Aquamin®, a Multi-Mineral Natural Product from Red Marine Algae, as an Adjuvant Intervention for Mild Ulcerative Colitis and Ulcerative Colitis in Remission

Company or agency sponsoring the study:

The University of Michigan

Principal-Investigator:

James Varani, Ph.D., Department of Pathology, The University of Michigan

Study Coordinators:

Muhammed N Aslam, MBBS, MD, Department of Pathology, The University of Michigan

Almo Regazi, BS, Department of Internal Medicine, The University of Michigan

1.1 Key Study Information

You may be eligible to take part in a research study. This form contains important information that will help you decide whether to join the study. Take the time to carefully review this information. You should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others such as your family, friends, or other doctors about joining this study. If you decide to join the study, you will be asked to sign this form before you can start study-related activities. Before you do, be sure you understand what the research study is about.

A research study is different from the regular medical care you receive from your doctor. Research studies hope to make discoveries and learn new information about diseases and how to treat them. You should consider the reasons why you might want to join a research study or why it is not the best decision for you at this time.

Research studies do not always offer the possibility of treating your disease or condition. Research studies also have different kinds of risks and risk levels, depending on the type of the study. You may also need to think about other requirements for being in the study. For example, some studies require you to travel to scheduled visits at the study site in Ann Arbor or elsewhere. This may require you to arrange travel, change work schedules, find child care, or make other plans. In your decision to participate in this study, consider all of these matters carefully.

This research is studying the use of Aquamin to learn about how it affects gastrointestinal permeability which is the control of material passing from inside the gastrointestinal tract throughout the gut wall to the rest of the body. We aim to study this in people with ulcerative colitis (UC), irritable bowel syndrome that is diarrhea-predominant(IBS-D) and in healthy individuals. Aquamin® is listed as Generally Regarded as Safe (GRAS) by the FDA. To be on the GRAS list, the FDA requires the same quantity and quality of scientific evidence as is required to obtain approval of the substance as a food additive. This study will look at whether Aquamin®, taken daily for 90 days, will improve barrier function. Your health-related information, blood, and urine will be collected for this research study.

This study will require you to stop taking certain supplements and medications before and during the research study. However, if you have UC, standard medications used to control your colitis symptoms are allowed with the exception of antibiotics and corticosteroids such as prednisone. If you decide to be in the study, you should understand that some symptoms that were controlled by the medications you were taking may worsen.

There can be risks associated with joining any research study. The type of risk may impact whether you decide to join the study. For this study, some of these risks may include belching, indigestion, and nausea. More detailed information will be provided later in this document.

If you have UC or IBS-D, this study may offer some benefit to you by relieving some symptoms of your disease. More information will be provided later in this document.

We expect the amount of time you will participate in the study will be 90 days.

You can decide not to be in this study. Even if you decide to join the study now, you are free to leave at any time if you change your mind.

2. PURPOSE OF THIS STUDY

2.1 Study purpose:

UC is known to cause inflammation and ulcers in the large intestine, which affect the large intestine's ability to protect the body and absorb nutrients. Similarly, studies have demonstrated increased permeability in patients with IBS-D. In previous studies, research has shown that Aquamin® has caused potentially beneficial changes in the colon with no serious side effects. The purpose of this study is to determine if Aquamin® affects gastrointestinal permeability in healthy volunteers and in those with UC when taken for 90 days.

3. WHO MAY PARTICIPATE IN THE STUDY

Taking part in this study is completely **voluntary**. You do not have to participate if you don't want to. You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled.

3.1 Who can take part in this study?

Those who can take part in the study will be male or female volunteers, ages 18-80 year. Participants may be healthy volunteers or may have mild UC or stable UC in remission or with IBS-D.

3.2 How many people are expected to take part in this study?

Thirty people are expected to complete this substudy at The University of Michigan, 12 healthy, 12 with IBS-D and 12 with UC.

4. INFORMATION ABOUT STUDY PARTICIPATION

4.1 What will happen to me in this study?

The study includes a total of three visits. In the morning of the day before the second and third visits, you will start a twenty-four-hour at-home urine collection, finishing the collection the day of your second and third visits. During that time, you will fast for 8 hours before and first 8 hours during the urine collection (of 24 hours) except to drink a lactulose/mannitol (sugar) solution and water.

Your first visit will be a screening visit. Your eligibility will be reviewed and you will sign this informed consent document to show that you agree to participate in the study. You will be asked questions about your medical history and medications. Your vitals (blood pressure, pulse, and temperature) will be taken, and you will have a urine pregnancy test, if applicable. You may not take the following medicines or supplements for 30 days before Visit 2 of the study and during your entire participation in the study: calcium, magnesium, Vitamin D supplements(including a multi-vitamin), fiber supplements, NSAIDs (such as Aspirin, Motrin, etc.), steroids (such

as Prednisone), antibiotics, anti-diarrheal (such as Imodium), antispasmodics (such as Atropine and Alverine), antidepressants (such as Wellbutrin), or diuretics (such as antidiuretic hormone - ADH or Desmopressin). Your visit will be scheduled for 30 days after the last time you took any of these. You will be given a urine collection kit (with instructions to use at-home, on the day before your Visit #2, prior to your appointment) which will include the lactulose and mannitol which are dispensed by the pharmacy. You will be given a urine collection kit with instructions to use at-home on the day BEFORE your Visit #2. THE KIT will include the lactulose and mannitol which is dispensed by the pharmacy. You will collect your urine first thing in the morning following an overnight fast. You will continue to fast for another 8 hours, except for drinking the lactulose/mannitol solution and a small amount of water (up to 4 cups), and will collect all of your urine over a twenty-four-hour period in the jugs provided. The urine collection will be completed the morning of the clinic visit.

Visit #2 will include vitals, a review of your medications, the collection of blood samples (totaling to 14ml of blood, or about 3 teaspoons), measurement of your height/weight and a urine pregnancy test (if applicable). You will receive your prescribed capsules of Aquamin® at this visit. You will be given a food questionnaire to complete in the next 90 days and a capsule diary to record when you have taken your capsules. You will return your (at-home) collected urine and will receive a new kit to use on the day of your Visit #3.

Visit #3 will take place 90 days after your second visit. This visit will be the same as visit #2, except that you will return your empty bottles, dietary questionnaire, and the capsule diary, and will not receive a urine collection kit.

Prior to urine collection on both occasions, you have to fast for 8 hours and must avoid certain foods and beverages (the detailed information is provided on urine-collection instruction sheet; for example, avoid alcohol for 7 days, marijuana products and mannitol for 48 hours and artificial sweeteners or fructose containing foods for 24 hours prior to urine collection). You also have to record your liquid intake during this 24 hours' period. If you have ulcerative colitis or IBS-D, then you will be given a disease-related questionnaire (called IBDQ or IBS-QOL) to evaluate your disease status on Visits 2 & 3.

Your participation in the study will also include two monitoring phone calls or emails at days 30 and 60 to check for any side effects and to make sure that you are taking your capsules on schedule. You have to provide your active phone number and email address for communication during the study.

4.2 How much of my time will be needed to take part in this study?

Each visit will take about a half an hour. The at-home urine collection prior to your 2nd and 3rd visits will take twenty-four hours. The study period where you are taking the capsules is 90 days (approximately three months).

4.3 When will my participation in the study be over?

Your participation will end after Visit #3.

4.4 What will happen with my information and/or biospecimens used in this study?

With appropriate permissions, your biospecimens and collected information may also be shared with other researchers, here, around the world, and with companies.

Your identifiable private information or identifiable biospecimens may be stripped of identifiers and used for future research studies or distributed to another researcher for future research studies without additional informed consent.

4.5 What will happen if my study visits are delayed because of COVID-19?

If we need to cancel a visit because we are not seeing study subjects due to COVID-19 risks, you will have an additional 30-day supply of capsules mailed to you and your visit will be rescheduled once we are able to see study subjects again. We may do this extension up to three times for up to an additional 90 days. The study team does not believe that there are any additional risks for taking your capsules for 30-90 more days. We will keep checking for side effects by contacting you through email or phone calls, and we will be available for you to

contact us as well. You will have the same safety checks that you have been having throughout the study and these will be done every 30 days during the extension time. You will continue to do your log and questionnaire.

5. INFORMATION ABOUT STUDY RISKS AND BENEFITS

5.1 What risks will I face by taking part in the study? What will the researchers do to protect me against these risks?

The known or expected risks are: There are rare risks which may occur when taking the natural product for the 90-day period. You may experience an upset stomach, vomiting, stomach pain, belching, constipation or change in bowel habit, dry mouth, increased urination, loss of appetite or a metallic taste. Some of these common gastrointestinal symptoms "nausea, gas and bloating" including change in bowel habit are likely related to the study and will be considered as possible risks of the study. These common symptoms can also be observed in the study population (in patients with inflammatory bowel diseases or Irritable bowel syndrome) as disease-related symptoms.

Blood draw: May cause pain, bleeding, bruising, soreness, and a small chance of infection at the draw site. Blood draws are performed by a trained professional to minimize risk.

Reproductive Risks: Because it isn't known whether the natural product may affect an unborn baby, you should not become pregnant while on this study. You should also not nurse your baby while on this study. Women must agree to use appropriate birth control over the study period.

Acceptable forms of birth control include: hormonal (such as pill, IUD), barrier (such as condom, diaphragm), surgical, or abstinence.

If you become pregnant or think that you have become pregnant during the study, notify the study team immediately.

Lactulose and Mannitol Consumption:

Lactulose can commonly cause diarrhea for a short period of time. Mannitol may cause dehydration, but this is rare with a small amount like you are taking for the study.

Additionally, there may be a risk of loss to confidentiality or privacy. See Section 9 of this document for more information on how the study team will protect your confidentiality and privacy.

The researchers will try to minimize these risks by monitoring adverse events reported by participants on a weekly basis to ensure safety of all participants. As with any research study, there may be additional risks that are unknown or unexpected.

5.2 What happens if I get hurt, become sick, or have other problems as a result of this research?

The researchers have taken steps to minimize the risks of this study. Even so, you may still have problems or side effects, even when the researchers are careful to avoid them. Please tell the researchers listed in Section 10 about any injuries, side effects, or other problems that you have during this study. You should also tell your regular doctors**.**

5.3 If I take part in this study, can I also participate in other studies?

Being in more than one research study at the same time, or even at different times, may increase the risks to you. It may also affect the results of the studies. You should not take part in more than one study without approval from the researchers involved in each study.

5.4 How could I benefit if I take part in this study? How could others benefit?

If you have UC, this study may offer some benefit to you now relieving some symptoms of your UC as well as extending the time of remission. People with UC may benefit from the knowledge gained from this study.

5.5 Will the researchers tell me if they learn of new information that could change my willingness to stay in this study?

Yes, the researchers will tell you if they learn of important new information that may change your willingness to stay in this study. If new information is provided to you after you have joined the study, it is possible that you may be asked to sign a new consent form that includes the new information.

6. ALTERNATIVES TO PARTICIPATING IN THE STUDY

6.1 If I decide not to take part in this study, what other options do I have?

You may withdraw from the study at any time and this will not affect your care at Michigan Medicine.

7. ENDING THE STUDY

7.1 If I want to stop participating in the study, what should I do?

You are free to leave the study at any time. If you leave the study before it is finished, there will be no penalty to you. You will not lose any benefits to which you may otherwise be entitled. If you choose to tell the researchers why you are leaving the study, your reasons for leaving may be kept as part of the study record. If you decide to leave the study before it is finished, please tell one of the persons listed in Section 10 “Contact Information”.

7.2 Could there be any harm to me if I decide to leave the study before it is finished?

No harm will come to you from leaving the study early. Your participation is voluntary.

7.3 Could the researchers take me out of the study even if I want to continue to participate?

Yes. There are many reasons why the researchers may need to end your participation in the study. Some examples are:

- The researcher believes that it is not in your best interest to stay in the study.
- You become ineligible to participate.
- Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- You do not follow instructions from the researchers.
- The study is suspended or cancelled.

8. FINANCIAL INFORMATION

8.1 Who will pay for the costs of the study? Will I or my health plan be billed for any costs of the study?

There is no cost to you or your insurance for participating in the study. By signing this form, you do not give up your right to seek payment if you are harmed as a result of being in this study.

If you are injured or in the event of a medical emergency, dial 911 or visit your nearest Emergency Room. If you believe the study has made you sick or caused you injury, contact one of the people listed in section 10 of this document (Contact Information). If taking part in the study makes you sick or causes you injury, you will have to arrange for treatment on your own, as the study will not provide medical treatment or provide any compensation to you. You or your insurance provider will be billed for all costs of treatment for sickness or injury caused by the study. It is possible that your insurance will not cover these costs.

By signing this form, you do not give up your right to seek payment if you are harmed as a result of being in this study.

8.2 Will I be paid or given anything for taking part in this study?

You will receive $20 after completion of Visit #2, and $40 after completion of Visit #3 and finishing of all the questionnaires in a timely fashion.

8.3 Who could profit or financially benefit from the study results?

The company whose product is being studied could, potentially, benefit from the study if the published results suggested that the product did, in fact, have beneficial effects.

Research can lead to new discoveries, such as new tests, drugs, or devices. Researchers, their organizations, and other entities, including companies, may potentially benefit from the use of the data or discoveries. You will not have rights to these discoveries or any proceeds from them.

9. CONFIDENTIALITY OF SUBJECT RECORDS AND AUTHORIZATION TO RELEASE YOUR PROTECTED HEALTH INFORMATION

The information below describes how the confidentiality of your research records will be protected in this study, and any sub-studies described in this document.

9.1 How will the researchers protect my information?

Every effort will be made to keep your personal information confidential. No mention of your name or other identifying information will be published. All of the other information collected about you during the study will be kept in a research record. We shall keep your research record confidential to the extent provided by federal, state and local law. We shall not allow anyone to see your record other than people who have a right to see it. All research records will be kept in a locked file cabinet or electronically, and computer storage is password-protected and access is restricted to the study team. No information is stored on portable devices.

During required reviews, representatives of the University of Michigan Medical Center or its representatives and/or the Food and Drug Administration (FDA) may possibly inspect your records.

A description of this clinical trial will be 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 website will include a summary of the results. You can search this website at any time.

9.2 What protected health information (PHI) about me could be seen by the researchers or by other people? Why? Who might see it?

Signing this form gives the researchers your permission to obtain, use, and share information about you for this study, and is required in order for you to take part in the study.

Medical information and billing records are protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA). This type of information is called protected health information (PHI). PHI about you may be obtained from any hospital, doctor, and other health care provider involved in your care, including:

- Hospital/doctor's office records, including test results (X-rays, blood tests, urine tests, etc.)
- HIV/AIDS status
- Sexually transmitted disease and/or other communicable disease status
- All records relating to your condition, the treatment you've received, and your response to the treatment
- Demographic information
- Personal identifiers

There are many reasons why information about you may be used or seen by the researchers or others during or after this study. Examples include:

- The researchers may need the information to make sure you can take part in the study.
- The researchers may need the information to look for side effects.
- University, Food and Drug Administration (FDA) and/or other government officials, auditors, and/or the IRB may need the information to make sure that the study is done in a safe and proper manner.
- Safety monitors or committees may need the information to:
    - Make sure the study is done safely and properly
    - Learn more about side effects
- The researchers may need to use the information to create a databank of information about your condition or its treatment.
- Information about your study participation may be included in your regular UMHS medical record.
- If you receive payment of $600 or more for taking part in this study, the University of Michigan accounting department will collect your name, address, Social Security number, payment amount, and related information. For tax reporting purposes, this information must be sent to the Internal Revenue Service (IRS).
- Federal or state law may require the study team to give information to government agencies. For example, to prevent harm to you or others, or for public health reasons.

The results of this study could be published in an article, but would not include any information that would let others know who you are.

9.3 What happens to information about me after the study is over or if I cancel my permission to use my PHI?

As a rule, the researchers will not continue to use or disclose information about you, but will keep it secure until it is destroyed. Sometimes, it may be necessary for information about you to continue to be used or disclosed, even after you have cancelled your permission or the study is over.

Examples of reasons for this include:

- To avoid losing study results that have already included your information
- To provide limited information for research, education, or other activities. (This information would not include your name, social security number, or anything else that could let others know who you are.)
- To help University and government officials make sure that the study was conducted properly

As long as your information is kept within the University of Michigan Health System, it is protected by the Health System's privacy policies. For more information about these policies, ask for a copy of the University of Michigan "Notice of Privacy Practices". This information is also available on the web at http://www.uofmhealth.org/patient+and+visitor+guide/hipaa. Note that once your information has been shared with others as described under Question 9.2, it may no longer be protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA).

9.4 When does my permission to use my PHI expire?

Your permission expires at the end of the study, unless you cancel it sooner. You may cancel your permission at any time by writing to the researchers listed in Section 10 "Contact Information" (below). If you withdraw your permission, you may no longer be eligible to participate in this study.

10. CONTACT INFORMATION

10.1 Who can I contact about this study?

Please contact the researchers listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Talk about study-related costs to you or your health plan
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator: James Varani, PhD
Mailing Address: Department of Pathology, University of Michigan, MSRB I, 4510 E, Ann Arbor, MI 48109
Telephone: (734) 615-0298

Medical Director: Danielle Kim Turgeon, MD
Mailing Address: 1500 E. Medical Center Drive, 3912 TC, Ann Arbor MI 48109-5362
Telephone: (734) 936-6267; please state that you are on the "Aquamin study" (For twenty-four-hour emergency reporting)

Study Coordinators:

Muhammed N Aslam, MBBS, MD
Mailing Address: Dept of Pathology, University of Michigan, MSRB I, Room 7510 D, Ann Arbor, MI 48109
Telephone: (734) 936-1897

Almo Regazi, BS
Mailing Address: 52 Simpson Memorial Institute, 102 Observatory, Ann Arbor, MI 48109
Telephone: (734) 647-9994

You can also contact study team at (734) 926-9011 or seaweed-study@med.umich.edu.

You may also express a question or concern about a study by contacting the Institutional Review Board listed below:

University of Michigan Medical School Institutional Review Board (IRBMED)
2800 Plymouth Road
Building 520, Room 3214
Ann Arbor, MI 48109-2800
Telephone: 734-763-4768 (For International Studies, include the appropriate calling codes.)
Fax: 734-763-1234
e-mail: irbmed@umich.edu

If you are concerned about a possible violation of your privacy or concerned about a study you may contact the University of Michigan Health System Compliance Help Line at 1-866-990-0111.

When you call or write about a concern, please provide as much information as possible, including the name of the researcher, the IRBMED number (at the top of this form), and details about the problem. This will help University officials to look into your concern. When reporting a concern, you do not have to give your name unless you want to.

11. RECORD OF INFORMATION PROVIDED

11.1 What documents will be given to me?

Your signature in the next section means that you have received a copy of this "Consent to be Part of a Research Study". (*Note: In addition to the copy you receive, copies of this document will be stored in a separate confidential research file and entered into your regular University of Michigan medical record.)*

12. SIGNATURES

Consent to Participate in the Research Study

I understand the information printed on this form. I have discussed this study, its risks and potential benefits, and my other choices with _____. My questions so far have been answered. I understand that if I have more questions or concerns about the study or my participation as a research subject, I may contact one of the people listed in Section 10 (above). I understand that I will receive a copy of this form at the time I sign it and later upon request.

□ Yes, I would like to be contacted regarding future studies.

□ No, I would not like to be contacted regarding future studies.

Print Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Consent to save samples for Unspecified Future Research and future participation

This project involves the option to allow the study team to keep your coded specimens/data for use in future research. I understand that it is my choice whether or not to allow future use of my specimens

_____ *Yes, I agree to let the study team keep my specimens for future research.*

_____ *No, I do not agree to let the study team keep my specimens for future research.*

You have the option of allowing the study team to contact you in the future regarding future research study. You can choose now to be re-contacted, but will have the option of saying no when re-contacted.

_____ *Yes, I would like to be contacted regarding future research.*

_____ *No, I do not want to be contacted for future research.*

Phone or email: _____

Print Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Principal Investigator or Designee
I have provided this participant with information about this study that I believe to be accurate and complete. The participant indicated that he or she understands the nature of the study, including risks and benefits of participating.

Print Legal Name: _____

Title: _____

Signature: _____

Date of Signature (mm/dd/yy): _____