Title: A Multicenter Randomized, Double-Blind, Placebo-controlled, Dosing, Safety, and Efficary Study of IMM 124-E (Hyperimmune Bovine Colostrum) for Patients with Severe Alcoholic Hepatitis.

NCT #: NCT01968382

Document approval date: August 10, 2017

Document Type: Informed Consent

RESEARCH PARTICIPANT INFORMATION AND CONSENT FORM

TITLE: A Multicenter Randomized, Double-Blind, Placebo-controlled Dosing, Safety and Efficacy Study of IMM 124-E (Hyperimmune Bovine Colostrum) for Patients with Severe Alcoholic hepatitis

VCU IRB PROTOCOL NUMBER: HM20000157

INVESTIGATOR: **Arun J. Sanyal MD**
Virginia Commonwealth University
Suthat Liangpunsakul MD
Indiana University
Vijay Shah MD
Mayo Clinic Rochester

SPONSOR: **National Institute on Alcohol Abuse and Alcoholism**
Secondary Sponsor: Immuron Ltd.
19 Kavanaugh Street
Southbank, VIC 3006, Australia

If any information contained in this consent form is not clear, please ask the study doctor or the study staff to explain any information that you do not fully understand. You will be provided an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

In this consent form, "you" always refers to the research participant. If you are a legally authorized representative, please remember that "you" refers to the study participant.

PURPOSE OF THE STUDY

The purpose of this research study is to test the safety, tolerability, and effectiveness of Imm 124-E (Bovine Colostrum Drug Substance or BCDS) when used to treat severe alcoholic hepatitis. You are being asked to participate in this study because you have been diagnosed with severe alcoholic hepatitis and may meet the study entry requirements.

Alcoholic hepatitis causes jaundice (yellowing of the skin and eyes), right sided upper abdominal pain, enlarged liver, and fever. The way that alcoholic hepatitis develops is not completely understood. It is believed that a chemical called lipopolysaccharide (LPS) which is produced by the body is the driving force behind this illness. Imm 124-E acts by binding LPS in your intestinal tract, thus lowering the levels of this chemical in the body. Drugs called steroids are the current treatment for alcoholic hepatitis. You will be prescribed these steroid drugs by your doctor since this is the established way that this illness is treated and we do not know yet if Imm124-E will be effective.

DESCRIPTION OF THE STUDY
Imm124-E is an investigational drug, which means it has not been approved by the U. S. Food and Drug Administration (FDA). We have permission from the FDA to use this drug for this clinical trial. In this study, we will compare two different doses of Imm124-E to placebo (a look-alike inactive substance).

Your participation in this study will last up to six months. Two other universities are involved in this study: Indiana University, Indianapolis, and Mayo Clinic, Rochester. A total of 66 individuals will participate in this study here and at the other two sites.

If significant new findings develop during the course of the research which may relate to your willingness to continue participation, this information will be provided to you.

PROCEDURES
If you decide to be in this research study, you will be asked to sign this consent form after you have had all your questions answered.

At your first study visit (Visit 1), your medical history will be taken, a physical exam will be performed, and a record of medications that you are taking will be made. The physical exam will include measurements of your height, weight and vital signs (pulse, blood pressure and temperature). Measurements of your waist, hips, and arm will be done as part of an overall nutrition assessment. Blood samples will be collected for routine lab tests. Approximately 3 tablespoons of blood will be collected. Women of childbearing potential will have a pregnancy test done. We will ask you to complete questionnaires about your alcohol use, your quality of life, your sleep habits, and tobacco and marijuana use.

Research study samples will be collected at this visit. These include a stool sample and urine sample; two tablespoons of blood will be drawn for research purposes.

If you meet entry criteria and still agree to participate, you will start study medication in addition to the steroid medication that you are already taking. Abstinence from alcohol should be maintained during your participation in the study and is essential in the prevention of the progression of your liver disease.

You will be randomly assigned (like the flip of a coin) to receive either:

- Imm124-E 2400 mg a day
- Imm124-E 4800 mg a day
- Placebo

The study drug will be taken as a powder, mixed with four tablespoons of water in a cup, with two packets of the study drug provided, twice a day. The study drug will need to be mixed gently in a cup and then you will drink the entire contents. Additional water may be added to the cup to ensure all the powder has been taken.

You have one chance in three of being assigned to placebo, and two chances in three of receiving either Imm124-E 2400 mg a day or 4800 mg a day. You will take the study

drug for 4 weeks (28 days). You will be instructed on when and how to take the study drug. You will be instructed not to discard any study drug or any empty packets but to return all to the study coordinator at your study visits.

Neither you nor the study doctor will know which study drug you are receiving. This information is available to the study doctor if needed in an emergency. This is done (blinding) so that a fair evaluation of results may be made.

Visit 2 will take place 7 days after Visit 1. You may still be in the hospital at the time of this visit. If you have been discharged, you will be scheduled to see the doctor and the study coordinator on the Clinical Research Services Unit (CRSU). Research samples consisting of about two tablespoons of blood will be drawn at this visit in addition to any routine labs ordered for your care. Urine and stool samples will also be collected. The doctors will evaluate your medical condition at this visit by using your lab results to determine if you are responding to treatment. If you are not responding, then the drug may be discontinued. You will have a physical exam, weight and vital signs, a medication review, and if you are a woman of childbearing potential, another urine pregnancy test will be done.

Visit 3 will be scheduled 28 -30 days after Visit 1. You will be asked about your health since the last visit and you will have a physical exam, weight, and vital signs. Research samples and routine labs will be collected as they were during your first visit. These include taking about two tablespoons of blood for research samples and about 3 tablespoons for standard lab work, and collecting urine and stool samples. If you are still on study drug, it will be discontinued at this visit. You should bring **all** of your remaining study drug supply to the research clinic. This includes any empty drug packets that you may have. We will review your other medications with you and make a record of these also. If you are a woman of childbearing potential, another urine pregnancy test will be done.

Visit 4 will take place about 90 days after Visit 1. Your medications will be reviewed as well as any changes in your health since your last visit. You will have a physical exam which will include weight, and vital signs. Routine standard of care lab work will be done. If you are a woman of childbearing potential, another urine pregnancy test will be done.

Visit 5, the last visit for this clinical trial, will be scheduled 180 days (about 6 months) after Visit I and will include a physical exam, weight, vital signs, and hip and waist, and arm measurements. Routine labs will be drawn as part of your regular care. Research samples will be collected. This includes about 2 tablespoons of blood, a urine sample, and a stool sample. You will be asked about your health since your last visit and a record will be made of your current medications. We will ask you to complete questionnaires about your alcohol use, your quality of life, your sleep habits, and tobacco and marijuana use. These are the same questionnaires that you completed at Visit 1.

The doctor may ask you to come in for a clinic visit anytime during the 180 study days if he thinks that you need a closer follow up for your care. You may request an extra appointment at any time that you feel you need to be seen by the doctor.

Liver biopsies will not be performed specifically for this research study. However, if you have had a liver biopsy, we will use that data as part of this study. Should you have a liver biopsy in the future, we will request that a small piece of the biopsy sample, if it is available, be used for research purposes. Only extra available liver tissue will be used so there is no increased risk to you during this procedure or in making a correct diagnosis of your liver disease. We will explain that to you more if and when you do have a liver biopsy.

You may be asked to participate in another study after you have completed this one. Would you like to be contacted for that study?

Yes No _____
Initial

RISKS AND DISCOMFORTS

Imm124-E is marketed in Australia under the brand name "Travelan". It is used for traveler's diarrhea. One hundred forty thousand packets (30 tablets per packet) have been sold over the counter to adults and children over age 6. No adverse effects have been reported by the Australian regulatory board.

Possible side effects associated with the use of Imm124-E include:

- Nausea and vomiting
- Abdominal pain
- Diarrhea
- Intestinal gas/bloating

Allergic reaction to Imm124- E is possible. Severe allergic reactions can be life threatening. There may be other unknown effects from Imm124-E, but the likelihood is low.

Your condition may not get better or may become worse while you are in the study.

As the study procedures might injure an unborn child, pregnant women may not participate. Women who might become pregnant should use a medically accepted form of birth control such as total abstinence, birth control pills, an IUD, diaphragm, progesterone injections or implants, or condoms plus a spermicide. Methods of birth control other than total abstinence are not 100% effective, and should a women become pregnant there may be risk of injury to an unborn child. For similar reasons, women who are nursing an infant may not participate.

For men, the study procedures might increase the risks for birth defects of any child conceived during treatment and several months after treatment is stopped. Men in this study who have the potential of fathering children should be aware of this possibility and consider using a medically accepted form of birth control.

Only the study participant can take the study drug. It must be kept out of the reach of children and persons who may not be able to read or understand the label.

The following risks may be associated with the study:

- Blood draw: the risks of the blood draw include slight pain, bruising, fainting, and rarely, infection. Trained people will perform the blood collection
- Questionnaires: One of the risks associated with answering questions is loss of confidentiality. Every effort will be made to keep personal information confidential. You will be assigned a study code so that it is unlikely to trace back to who you are based on your background/questionnaire information. You might also feel uncomfortable answering some of the questions. You do not have to answer any questions that you are not comfortable answering.
- Physical examination: There is no significant risk associated with physical examination.

USE AND DISCLOSURE OF PROTECTED HEALTH INFORMATION

Authority to Request Protected Health Information

The following people and/or groups may request my Protected Health Information:

- Principal Investigator and Research Staff
- Research Investigators at other sites involved in this study
- Data Safety Monitoring Boards
- Study Sponsor (NIAAA)
- Institutional Review Boards
- Food and Drug Administration
- Department of Health and Human Services

Authority to Release Protected Health Information

The VCU Health System (VCUHS) may release the information identified in this authorization from my medical records and provide this information to:

- Health Care Providers at the VCUHS
- Study Sponsor (NIAAA)
- Food and Drug Administration
- Data Coordinators
- Data Safety Monitoring Boards
- Principal Investigator and Research Staff Research Investigators at other sites involved in this study
- Institutional Review Boards
- Department of Health and Human Services

Once your health information has been disclosed to anyone outside of this study, the information may no longer be protected under this authorization. An example of this is if you request your information such as test results be released to your primary care physician, then this authorization does not assure their confidentiality.

Type of Information that may be Released

The following types of information may be used for the conduct of this research:

☒ Complete health record
☒ Diagnosis & treatment codes
☒ Discharge summary
☒ History and physical exam
☒ Consultation reports
☒ Progress notes
☒ Laboratory test results
☒ X-ray reports
☒ X-ray films / images
☐ Photographs, videotapes
☐ Complete billing record
☐ Itemized bill
☒ Information about drug or alcohol abuse
☒ Information about Hepatitis B or C tests
☐ Information about psychiatric care
☐ Information about sexually transmitted diseases
☐ Other (specify):

Expiration of this Authorization

☐ This authorization will expire when the research study is closed, or there is no need to review, analyze and consider the data generated by the research project, whichever is later.
☒ This research study involves the use of a Data or Tissue Repository (bank) and will never expire.
☐ Other (specify):

Right to Revoke Authorization and Re-disclosure

You may change your mind and revoke (take back) the right to use your protected health information at any time. Even if you revoke this Authorization, the researchers may still use or disclose health information they have already collected about you for this study. If you revoke this Authorization you may no longer be allowed to participate in the research study. To revoke this Authorization, you must write to the Principal Investigator.

BENEFITS TO YOU AND OTHERS

During this study, you will receive steroid medications which is the current treatment for alcoholic hepatitis. IMM 124-E may be beneficial to you in addition to the use of steroid drugs. However, this benefit cannot be guaranteed. It is not known if IMM 124-E will be harmful but it is unlikely. You will be carefully monitored while taking this medication and it can be discontinued at any time during the 28 days that you will receive it.

COSTS

Study drug will be provided by the sponsor. There are no charges for clinic visits related to this study. Samples drawn for research study purposes will be covered. Any tests, which include laboratory tests done as part of your routine medical care, will not be covered by this study. This will be billed to your insurance. If your insurance does not pay, then you will be responsible for the cost. Having a liver biopsy is not part of this study so should you undergo a liver biopsy, it will be billed to your insurance company.

ALTERNATIVE TREATMENT

You do not have to participate in this study to receive treatment for alcoholic hepatitis because you will be treated with steroid medications which is the standard treatment. In this study, you will be receiving study drug or placebo in addition to the steroid medications if you choose to participate. The study doctor will discuss this with you. Your disease is directly caused by excessive alcohol consumption. Abstinence is essential in the prevention of the progression of your liver disease.

CONFIDENTIALITY

As with all research, there is a chance that confidentiality could be compromised; however, we take precautions to minimize the risk. Potentially identifiable information about you will consist of blood samples, urine samples, stool samples, questionnaires, and data extracted from your medical records. Data are being collected only for research purposes. Study records that identify you will be kept confidential. You will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records disclosed outside this institution. You understand that the results of the research study may be published in medical journals, but that your name or identity will not be revealed and that your record will remain confidential. A study code number will be used to keep track of your files in an anonymous manner. All personal identifying information will be kept in password protected files and these files will be stored for 15 years, or until after the study is complete, whichever is longer. Other records such as doctors' notes, lab results, and x-ray reports will be stored indefinitely. Access to all data will be limited to study personnel.

As part of this study, your doctor and the study staff will ask you to have certain tests. Some of these blood and urine tests would have been done as part of your regular care. They will use these test results to both treat you and to complete this research.

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.

DATA REGISTRIES

Your doctor will collect several samples of bio-specimens (consisting of blood, urine, and stool samples) from you during this study. The test results from these samples are for research purposes only. The testing is being conducted for exploratory research purposes only and has no clear implications about you or your family medical conditions.

Some of your samples will be stored at Indiana Biobank, a Specimen Storage Facility, supported by the National Institutes of Health. The purpose of this collection is to have samples available for use in research and clinical factors related to your disease even after the current study is completed. Storing samples may provide researchers with valuable material that can help them to develop new diagnostic tests, new treatments, and new

ways to prevent disease. All specimens will be labeled with an identification number and the date your sample was collected. Your name will not be on any blood, urine, and stool samples and the "key" which links your identity to your samples will be stored separately and securely at VCU. Your blood sample will be stored for as long as possible and will be used in future testing. The research studies in which the specimens may be used have not yet been fully determined.

If you decide at any time during the research study that you would like to withdraw your samples from the study, you will need to put your request in writing to the study doctor or study team. Your samples will be removed from the Indiana Biobank. You will receive written notification when this has been done.

Other researchers at VCU who aren't involved with this study may ask to use your sample for future research. Researchers at other institutions may also ask for a part of your sample for future studies. Your samples will be sent to researchers in a coded format, which protects your identity.

1. I give permission for my data/tissue samples collected at VCU Medical Center to be stored at the Indiana Biobank and used for future research related to liver disease or research on any major disease, health condition or risk factor.

YES NO _____ _____
Initial Date

2. I give permission to VCU Medical Center to give my samples which have been collected at VCU Medical Center and stored at the Indiana Biobank to other researchers at other institutions to be stored and used in future research related to liver disease or research on any major disease, health condition, or risk factor.

YES NO _____ _____
Initial Date

COMPENSATION FOR INJURY or ILLNESS

If you are injured by, or become ill, from participating in this study, please contact your study doctor immediately. Medical treatment is available at the Virginia Commonwealth University Health System (VCU Health System). Your study doctor will arrange for short-term emergency care at the VCU Health System or for a referral if it is needed.

Fees for such treatment may be billed to you or to appropriate third party insurance. Your health insurance company may or may not pay for treatment of injuries or illness as a result of your participation in this study.

To help avoid research-related injury or illness it is very important to follow all study directions.

VOLUNTARY PARTICIPATION AND WITHDRAWAL
Your participation in this study is voluntary. You may decide to not participate in this study. Your decision not to take part will involve no penalty or loss of benefits to which you are otherwise entitled. If you do participate, you may freely withdraw from the study at any time. Your decision to withdraw will involve no penalty or loss of benefits to which you are otherwise entitled.

Your participation in this study may be stopped at any time by the study doctor or the sponsor without your consent. The reasons might include:
- the study doctor thinks it necessary for your health or safety;
- you have not followed study instructions;
- the sponsor has stopped the study; or
- administrative reasons require your withdrawal.

If you leave the study before the final regularly scheduled visit, we may ask you to come in to see the doctor and study coordinator for an early close out visit.

If you decide to stop participating in this study, your samples will no longer be provided to researchers and no more data will be collected. However, any research already conducted on your samples and information collected will remain part of the research project using them unless you wish to request in writing that your samples and data be destroyed. You can provide a written request to any investigator in this study.

QUESTIONS
If you have any questions, complaints, or concerns about your participation in this research, contact:

Dr. Arun Sanyal
and/or
Dr. Velimir Luketic, Dr. M. Shadab Siddiqui

At 804-828-4060, 24 hours 7days/week.

Or you may contact your study coordinator at the same number.
You may write to your study doctor at the following address:

Dr. Arun Sanyal
VCU Medical Center
1200 East Broad Street
Room 1490
Box 980341
Richmond, VA 23298

The researcher/study staff named above is the best person(s) to call for questions about your participation in this study.

If you have general questions about your rights as a participant in this or any other research, you may contact:

Office of Research
Virginia Commonwealth University
800 East Leigh Street, Suite 3000
Box 980568
Richmond, VA 23298
Telephone: (804) 827-2157

Contact this number for general questions, concerns, or complaints about research. You may also call this number if you cannot reach the research team or if you wish to talk to someone else. General information about participation in research studies can also be found at http://www.research.vcu.edu/irb/volunteers.htm
Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

CONSENT

I have been provided with an opportunity to read this consent form carefully. All of the questions that I wish to raise concerning this study have been answered.

By signing this consent form, I have not waived any of the legal rights or benefits, to which I otherwise would be entitled. My signature indicates that I freely consent to participate in this research study. I will receive a copy of the consent form once I have agreed to participate.

_____
Participant Name, printed

_____ _____
Participant Signature Date

_____ _____
Name of Legally Authorized Representative (Printed) Relationship to Participant

_____ _____
Legally Authorized Representative Signature Date

_____
Name of Person Conducting Informed Consent Discussion / Witness
(Printed)

_____ _____
Signature of Person Conducting Informed Consent Discussion / Witness Date

_____ _____
Investigator Signature (if different from above) Date