Affix Patient Label Here

CONSENT TO PARTICIPATE IN RESEARCH
MT2021-01/2021LS006

Title of Research Study: *PTCy + Sirolimus/VIC-1911 as GVHD prophylaxis in myeloablative PBSC transplantation*

Investigator Team and Contact Information:

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Funding Information: This study was developed by Dr. Shernan Holtan at University of Minnesota and is funded by Vitrac Therapeutics.

Clinical Trial Questions and Answers

Key Information About this Research	
Why am I being asked to participate in this research?	You are invited to participate in this research study because you are planning to undergo a stem cell transplant. To be considered for this study you must be over the age of 18. The study is a clinical trial of a new drug (VIC-1911) that may help prevent both relapse and graft-versus-host disease (GVHD) based upon laboratory experiments performed at the University of Minnesota.
Why is this research being done?	The purpose of this study is to learn whether a 40-day course of the study drug VIC-1911 is a safe and effective method of preventing both GVHD and relapse in adults undergoing stem cell transplantation.
How long will I be in the study?	We expect that you will be in this research study for about 13 months. The first month will include pre-treatment evaluations and the stem cell transplant. You will have your first dose of study drug 5 days after the stem cell transplant and continue taking it through 45 days after transplant (day +5 through day +45). Standard supportive care GVHD prevention drugs and follow-up exams will continue through 1 year post transplant.
What will I need to do to participate?	You will be asked to undergo a standard transplant conditioning regimen of total body irradiation two times a day for four days OR chemotherapy with busulfan and fludarabine depending on what your treating physician decides is best for you, then stem cell infusion, standard supportive GVHD prevention drugs of cyclophosphamide and sirolimus, and treatment with VIC-1911. Throughout the study you will be evaluated for side effects, these evaluations will include visits with an eye doctor. You will be asked to return to the clinic frequently for three

	months post-transplant, then at six months and 1 year, for follow up tests. You will be asked to fill out quality of life surveys. All visits and lab draws will be done in conjunction with your routine clinic visits. Please see **Appendix I** for a study calendar.
Could this study be bad for me?	• The most commonly experienced side effects of VIC-1911 include low blood cell counts, anemia, blurred vision, stomach upset, fatigue, muscle aches, abnormal liver and kidney function tests, headache, cough, and difficulty breathing. Please See **Appendix II** for a complete list of side effects that have been observed in studies on VIC-1911 Please See **Appendix III** for a detailed list of risks for the standard of care treatments.
Could this study help me?	There is no guarantee of benefit to you from your taking part in this research. This combination treatment may help prevent GVHD and prevent cancer relapse. However, in this study, we hope to learn what is the most appropriate dose of VIC-1911 that can be given with the long-term goal of finding effective preventative treatment for GVHD while also protecting patients from cancer relapse.
What happens if I do not want to be in this research? What are my alternatives?	You do not have to participate in this research study. Instead of being in this research study, your doctors will review the other possible treatment choices which may include: • standard of care treatment with GVHD preventative drugs • Other investigational treatments at this institution or at other research centers. Your doctors can provide you with additional information regarding your options.
Detailed Information About This Research Study	
How many people will be studied?	Up to 79 patients will be enrolled in this study.
What is the standard medical prevention for	GVHD occurs when the donor cells (the graft) see the patient's body cells (the host) as foreign and attacks them. Acute GVHD occurs within the first few months after the transplant. It may affect the skin (rash, itching), the gastrointestinal (GI) tract (severe diarrhea, pain, ulcers of the GI tract) and/or

this condition?	the liver (yellowing of the skin, worsening of liver function as detected by blood tests). Standard prevention of GVHD involves the use of at least 2 drugs to suppression the developing immune system. Despite the use of standard immunosuppressant drugs, some patients still experience GVHD after transplant. We also know that powerful immunosuppressant drugs also increase the risk of cancer relapse after a transplant. Therefore, we are trying to find a better combination of drugs that reduce the risk of GVHD while also decreasing the risk of post-transplant relapse.
What aspect of my care is research?	The only aspect of this trial that is research is the addition of the drug VIC-1911 from day +5 through day +45 to a standard GVHD prophylaxis regimen of cyclophosphamide and sirolimus. Patients who are not on this study would typically receive cyclophosphamide, sirolimus, and an immunosuppressant called mycophenolate mofetil (MMF), which helps reduce GVHD but does not help reduce relapse risk. In this study, VIC-1911 (a drug that helps reduce both GVHD and relapse in laboratory studies) is substituted for MMF. All other interventions on this study are standard treatments and supportive care for patients undergoing transplantation. Part 1 of this research is to determine the ***optimal*** dose of VIC-1911. Increasingly higher doses of VIC-1911 will be given to patients on this trial. The first patients who enroll on this this study will be given the lowest dose of the study drug. The researchers will take blood samples to test how your new immune system is responding to this drug. Patients who enroll on this study later will be given higher doses depending upon how the initial patients responded to this therapy until the researchers discover the safest and most effective dose. In part 2 of this study, all patients will be given the dose that was decided in part 1, in order to continue to test how effective the study drug is in preventing GVHD. While the U.S. Food and Drug Administration (FDA) has given permission to test the safety of VIC-1911, the study drug is not considered to be an approved treatment for general use; therefore, it is only available through a clinical research study conducted under an FDA Investigational New Drug (IND) application.
Is there any randomization or placebo in this study?	There is no randomization or placebo. All patients will receive the same standard of care stem cell transplant and supportive care. Up to 3 dose levels of VIC-1911 will be tested, with later patients receiving higher doses until most effective dose is determined. At the most effective dose, additional patients will be enrolled to assess the treatment's safety and effectiveness.

	You will be told which dose level you are to receive at the time of study enrollment as well as the safety information available from all prior patients.
What happens if I say "Yes, I want to be in this research"?	Prior to treatment, the Transplant Coordinator will verify your coverage with your insurance company to be sure that you are pre-authorized before beginning any part of this treatment. If you have concerns or questions regarding coverage or potential charges, you should contact the patient financial representative at (612) 273-2800. All research and clinical procedures, from screening through follow up are described in Appendix I. Additionally, you will be asked to permit us to save blood samples and your medical data regarding your treatment for use in future research as well as share data with agencies who have regulatory oversight.
What are my responsibilities?	• Taking the study drug, routine drugs, and eye drops as directed • Keeping track of your medication in a drug diary • Keeping your scheduled clinic appointments • Alerting your doctors to any changes in your health
Will it cost me anything to be in this research?	The VIC-1911 will be provided by the study and all collection of all research samples, eye examinations performed for your safety, and data collection will be paid for by study funds. You or your insurance company will be responsible for costs related to the standard of care portions of this treatment including but not limited to: the total body radiation; the costs of the cyclophosphamide and sirolimus; the stem cell transplant; the costs of the supplies necessary for dispensing the drugs; supportive care (drugs such as Tylenol); the hospitalization; clinic visits; routine lab work; and any medications given to prevent or treat side effects. You will be responsible for any costs your insurance does not cover, such as deductibles and co-payments. The blood and marrow transplant office will receive "prior authorization" from your insurance as part of your pre-treatment screening. Please see "**Additional Information about Clinical Trials in the Blood and Marrow Transplant Program at M Health Fairview"** for information about the costs of the standard clinical treatment.

Are there any research specimens collected as part of this study?

As this is a clinical research study, additional blood is collected for research related testing (60 ml or about 4 tablespoons) at key time points throughout the study as summarized in the table below. The research samples will be collected at the time blood is drawn for routine medical care whenever possible. The table does not represent all the times blood is collected for routine care, only those time points where blood also is collected for research purposes.

Time point	**Approximate Blood volume**	
	Research	**Routine (standard of care)**
This sample was taken during screening for eligibility.	4 tablespoons	1 – 3 tablespoons depending if research sample is collected during screening or at hospital admission
Before the donor cell infusion (Day 0)		½ to 1 tablespoon depending of level of blood testing
Once a week for the 1st 6 weeks after the transplant		½ to 1 tablespoon depending of level of blood testing
1 month after transplant	4 tablespoons	
2 and 3 months after the transplant	4 tablespoons	½ to 1 tablespoon depending of level of blood testing

At the time you are having a bone marrow biopsy as part of your medical care; an additional sample (approximately 2 tablespoons) will be collected for research purposes.

Will I receive research test results?

Because it is not known how soon these samples will be used, you will not be given the results of the tests. Most tests done on samples in research studies are only to learn more about the GVHD response to treatment or general research on GVHD.

What happens to the data/ specimens collected for research?	Vitrac Therapeutics, the manufacturer of VIC-1911 will receive copies of any product related reports submitted to the FDA. There may be some leftover blood cells from the samples collected for research purposes. With your permission, we would like to store them for up to 15 years after the study ends for future analysis as new research tests become available. These samples will be the property of the Principal Investigator Punita Grover, MD. Data/Specimens may be shared with researchers/institutions outside of University of Minnesota. This could include for profit companies. We will not ask for your consent before using or sharing them. We will remove identifiers from your data and/or specimens, which means that nobody who works with them for future research will know who you are. Therefore, you will not receive any results or financial benefit from future research done on your specimens or data. The samples will be stored with indirect identifiers. They will be labeled with a unique code number, rather than a name or medical record number, and the samples can only be linked back to the patient using a master list for the study. This master list will be kept in a secured manner and only accessible to persons directly involved with the research. There will be no cost to you for storing and future testing of the leftover samples. You will not be paid for allowing your samples to be used for future research. Fifteen years after the end of the study any remaining samples will be destroyed. However, if you agree to storage now and later change your mind, you may request to have any remaining identifiable samples destroyed by contacting the study doctor or another member of the study staff.

Additional Information about Clinical Trials in the Blood and Marrow Transplant Program at M Health Fairview

If your doctor is also the person responsible for this research study, please note that s/he is interested in both your clinical care and the conduct of this research study. You have the right to discuss this study with another person who is not part of the research team before deciding whether to participate in the research.

Introduction to Clinical Trials	We invite you to join this clinical trial. A clinical trial is a study in humans to evaluate a medical treatment. Investigators use clinical trials to study whether a new treatment is safer and/or more effective than a standard treatment. ● The goal of research is to learn new things in order to help groups of people in the future. Investigators learn things by following the same plan with a number of participants, so they do not usually make changes to the plan for individual research participants. You, as an individual, may or may not be helped by volunteering for a research study. ● The goal of clinical care is to help you get better or to improve your quality of life. Doctors can make changes to your clinical care plan ("patient care plan") as needed. Research and patient care are often combined. This consent document is to provide you clear information about the specific **research activities** of this study.
What should I know about a research study?	• Someone will explain this research study to you. • Whether or not you take part is up to you. • You can choose not to take part. • You can agree to take part and later change your mind. • Your decision will not be held against you. • You can ask all the questions you want before you decide.
What happens if I do not want to be in this study; or, if I say yes but change my mind later?	Participation in this study is voluntary. You can say no to this study, or leave the research study at any time and no one will be upset by your decision. Choosing not to be in this study or to stop being in this study will not result in any penalty to you or loss of benefit to which you are entitled. This means that your choice not to be in this study or your choice to leave this study will not negatively affect your right to any present or future medical care. You may still receive medical care from this institution. If you decide to leave the research study, let your doctor know so he or she can

	tell you how to stop safely. Stopping treatment without "tapering" (slowly lowering the dose) the study drugs may cause you to experience withdrawal symptoms. We want to make sure that you are able to stop the study safely. We will also talk to you about follow-up care, if needed. If you stop being in the research, information already collected about you will not be removed from the study database. You will be asked whether the investigator can collect information from your routine medical care, such as your medical records. If you agree, this information will be handled the same as the information obtained for the research study.
What about pregnancy and fertility (if applicable)?	The procedures in this research are known to harm a pregnancy or fetus. You cannot be in this study (includes follow-up visits) if you are pregnant or nursing a child. You cannot be in this study if during the study you plan to become pregnant or will nurse a child. If you are a woman and it is possible for you to become pregnant, you must agree to use effective contraception while receiving the study drugs and for six months after the last dose. You must use two effective forms of birth control, one of which must be a barrier method. For example, use of intrauterine device (IUD) or oral contraceptives, plus a barrier method such as a condom, diaphragm or cervical cap. If you are male and it is possible for you to father a child, then you, and/or your partner must use adequate contraception while you are receiving the study drugs and for 30 days after the last dose. This is unless you have had a successful vasectomy with confirmed azoospermia (semen with no sperm). According to the World Health Organization and the United States Center for Disease Control and Prevention, the most effective forms of birth control include complete abstinence, surgical sterilization (both male and female), intrauterine devices (IUDs), and the contraceptive implant. The next most effective forms of birth control include injectables, oral contraceptive pills, the contraceptive ring, or the contraceptive patch. Acceptable, but least effective, methods of birth control include male condoms (with or without spermicide) and female condoms. If you or your partner [are/is] considered to be postmenopausal, you are not required to use contraception while participating in this research study. Postmenopausal women rarely become pregnant.

	If you or your partner become pregnant while participating in this research study, it is important that you tell the study doctor or other research team member immediately. You may be required to stop participation in this study; however, other clinical care options will be discussed with you at that time if necessary.
Will I be paid for being in this study?	No, you will not receive any payment for participation.
Will it cost me anything to be in this research?	You or your insurance company will be responsible for all costs related to standard treatment including but not limited to: supportive care (such as Tylenol); the hospitalization; clinic visits; routine lab work; and any medications given to prevent or treat side effects. You will be responsible for any costs your insurance does not cover, such as deductibles and co-payments. The transplant will receive "prior authorization" from your insurance as part of your pre-transplant screening. You and your insurance company will be charged for the health care services that you would ordinarily be responsible to pay. In some cases, insurance will not pay for services ordinarily covered because these services are performed in a research study. You should check with your insurance to see what services will be covered by your insurance and what you will be responsible to pay. All costs associated with this treatment will be billed to you and/or your health insurance/health plan in the usual way. Prior to transplant, the Transplant Finance Coordinator will verify your coverage with your insurance company to be sure that your care is approved before beginning any part of this study.
Would I ever be removed from the study by my doctors or the study team?	Your study doctor may discontinue your treatment on this study at any time with or without your consent. Treatment may be ended for a number of reasons, including: • You have side effects that the study doctor considers unacceptable despite changes in drug dose and/or schedule. • Your disease returns or worsens. • You require other anti-cancer treatments or you require treatment with drugs not allowed by this study. • Continuing on treatment, regardless of reason, is not in your best interest. • You are unable or unwilling to keep appointments.

What happens if I am injured while participating in this research?	In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner, to you or your insurance company. If you think that you have suffered a research related injury let the study physicians know right away.
New Information Available During the Study	If the study doctors learn new information about the risks and benefits of taking part in this clinical trial, they will tell you.
What happens to my information collected during this study?	Your privacy is very important to us. 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 confidentiality. Organizations that may inspect and copy your information include the Institutional Review Board (IRB), the committee that provides ethical and regulatory oversight of research, and other representatives of this institution, including those that have responsibilities for monitoring or ensuring compliance. The researchers will share your information, including research study records, only with people who need to review this information. This includes: • The Masonic Cancer Center, University of Minnesota and/or their designee. • Any person who provides services or oversight responsibilities in connection with this study. • Any member of the University of Minnesota workforce who provides services in connection with this study. • Any laboratories, individuals, and organizations that use your health information in connection with this study. • The Fairview BMT Database, a registry that compiles demographic and medical information related to hematopoietic cell transplant patients and donors. • Any federal, state, or local governmental agency that regulates the study (such as the U.S. Food and Drug Administration (FDA), the U.S. Department of Health & Human Services (DHHS), and the Office for Human Research Protections (OHRP)). • Center for International Blood and Marrow Transplant Research (CIBMTR) and National Marrow Donor Program (NMDP) for the Observational Research Database – this organization collects information on therapies involving donor cells. • The designated Protocol Review and Monitoring Committees, Institutional Review Boards (IRB) such as the University of Minnesota IRB, Privacy Boards,

	Data and Safety Monitoring Council and their related staff that have oversight responsibilities for this study. The sponsor, monitors, auditors, IRB, and regulatory authorities will be granted direct access to the subject's original medical records for verification of clinical trial procedures and data, without violating the confidentiality of the subject, to the extent permitted by applicable laws and regulations and that, by signing the consent document, the subject or LAR is authorizing such 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 at http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time. If we learn about any of the following, we may be required or permitted by law or policy to report this information to authorities: • Current or ongoing child or vulnerable adult abuse or neglect; • Communicable, infectious or other diseases required to be reported under Minnesota's Reportable Disease Rule; • Certain wounds or conditions required to be reported under other state or federal law; or • Excessive use of alcohol or use of controlled substances for non-medical reasons during pregnancy. Your PHI created or received for the purposes of this study is protected under the federal regulation known as HIPAA. Refer to the attached HIPAA authorization for details concerning the use of this information.
Privacy & confidentiality risks:	There is some risk of a data breach involving the information we have about you. We comply with the University's security standards to secure your information and minimize risks, but there is always a possibility of a data breach.

What happens to the genetic information?	A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways: • Health insurance companies and group health plans may not request your genetic information that we get from this research. • Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums. • Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment. Be aware that this federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.
I have more questions. Who can I talk to?	For questions about research appointments, the study, research results, or other concerns, call the study team at the contact information listed on page 1. This research has been reviewed and approved by an IRB within the Human Research Protections Program (HRPP). To share feedback privately with the HRPP about your research experience, call the Research Participants' Advocate Line at 612-625-1650 (Toll Free: 1-888-224-8636) or go to z.umn.edu/participants. You are encouraged to contact the HRPP if: ● Your questions are not being answered by the research team. ● You cannot reach the research team. ● You want to talk to someone besides the research team. ● You have questions about your rights as a research participant. ● You want to get information or provide feedback about this research.
Will anyone besides the study team be at my consent meeting?	You may be asked by the study team for your permission for an auditor to observe your consent meeting. Observing the consent meeting is one way that the University of Minnesota makes sure that your rights as a research participant are protected. The auditor is there to observe the consent meeting, which will be carried out by the people on the study team. The auditor will not document any personal (e.g. name, date of birth) or confidential information about you. The auditor will not observe your consent meeting without your permission ahead of time.

Will I have a chance to provide feedback after the study is over?	The HRPP may ask you to complete a survey that asks about your experience as a research participant. You do not have to complete the survey if you do not want to. If you do choose to complete the survey, your responses will be anonymous. If you are not asked to complete a survey, but you would like to share feedback, please contact the study team or the HRPP. See the "Investigator Contact Information" of this form for study team contact information and "Whom do I contact if I have questions, concerns or feedback about my experience?" of this form for HRPP contact information.

Optional Elements:

The following research activities are optional, meaning that you do not have to agree to them in order to participate in the research study. Please indicate your willingness to participate in these optional activities by placing your initials next to each activity.

Yes, I agree	**No, I disagree**	
_____	_____	The investigator may retain any leftover blood samples taken during the study. These samples may be used for other research not related to this study. These samples will be retained in non-identifiable form, meaning that there will be no information associated with the blood that will allow anyone to readily ascertain my identity.

Affix Patient Label Here

CONSENT TO PARTICIPATE IN RESEARCH
MT2021-01/2021LS006

Signature Block:

Your signature documents your permission to take part in this research. You will be provided a copy of this signed document.

_____
Printed Name of Participant

_____ _____
Signature of Participant Date Date

_____ _____
Signature of Person Obtaining Consent Date

_____
Printed Name of Person Obtaining Consent

APPENDIX I –STUDY PROCEDURES

Study Calendar

Treatment will be given in 3 parts – 1) a conditioning regimen of total body irradiation (TBI) or busulfan/fludarabine given over several days followed by 2) the transplant then 3) medicines to reduce or prevent GVHD.

Study Calendar: Participants Receiving Total Body Irradiation (TBI)

Day	Drug or Procedure	Dose Information
Conditioning Regimen		
-4, -3, -2, -1	TBI	Two times daily
Transplant		
0	Donor bone marrow cell (transplant)	infused over less than 1 hour
GVHD Preventative Drugs		
+3, +4	Cyclophosphamide	1 daily dose by IV over 1 to 2 hours
+5	Begin sirolimus	2 or 3 (depending on your body weight) daily doses IV* until day +100
+5	Begin VIC-1911 Eye drops	Twice daily pills through day +45 Twice daily eye drops through day +45

*After discharge, sirolimus will be given by mouth

Note about treatment day numbering with transplants: The day of the transplant is called day 0. Days before the transplant are indicated by a negative number and days after the transplant are indicated by a positive number (or no sign). This treatment begins on day -4 or 4 days before the day of the planned transplant.

VIC-1911 may damage your eyes, or make them feel uncomfortable, so you will be use eye drops every day while you are taking the study drug.

Study Calendar for Participants Recieving Busulfan and Fludarabine:

Day	Drug or Procedure	Dose Information
Conditioning Regimen		
-5, -4, -3, -2	Busulfan	130 mg/m^2 IV once daily over 3 hours
-5, -4, -3, -2	Fludarabine	40 mg/m^2 IV once daily
Transplant		
0	Donor bone marrow cell (transplant)	infused over less than 1 hour
GVHD Preventative Drugs		
+3, +4	Cyclophosphamide	1 daily dose by IV over 1 to 2 hours
+5	Begin sirolimus	2 or 3 (depending on your body weight) daily doses IV* until day +100
+5	Begin VIC-1911 Eye drops	Twice daily pills through day +45 Twice daily eye drops through day +45

Note about treatment day numbering with transplants: The day of the transplant is called day 0. Days before the transplant are indicated by a negative number and days after the transplant are indicated by a positive number (or no sign). This treatment begins on day -5 or 5 days before the day of the planned transplant.

VIC-1911 may damage your eyes, or make them feel uncomfortable, so you will be use eye drops every day while you are taking the study drug.

Follow-up and Care After the Transplant

Physical exams and blood tests will be done to check for blood count recovery and to look for side effects. During the first 2-3 weeks after the transplant, up to 2 tablespoons of blood will be drawn daily. Supportive care is given to all patients after a transplant. This may include transfusions of red blood cells or platelets, drugs to prevent or treat infections and drugs to help your bone marrow recover. You will be asked Quality of Life survey questions at day +21 and day +100.

Blood will be drawn less less often as your counts improve. After blood count recovery and discharge from the hospital, you will have at least weekly follow-up visits in the outpatient clinic for the 1st 3 months after the transplant.

Routine clinic follow-up is required at 6 and 12 months after the transplant with at least yearly contact (in person, by phone or mail) after that. You will have eye doctor visits at pre-transplant and at 1 and 3 months post-transplant, or as needed thereafter.

APPENDIX II – SERIOUS RISKS OF VIC-1911

Common (≥ 10%)	Less Common (≥ 5%)	Rare (≤ 2% or less)
• Anemia • Vision blurred • Abdominal pain/discomfort, nausea, vomiting, diarrhea, low appetite • Constipation • Fatigue, tiredness • Pain (back, side and muscle pain) • Urinary tract infection • Liver damage • Impaired kidney function • Elevated Lipase which can indicate pancreatitis or blocked pancrease • Weight loss • Headache • Cough • Dyspnea (difficulty breathing) • Rash and itching • Low blood pressure	• Eye pain, eye damage • Chest pain • Pain in extremity • fever • Upper respiratory tract infection • High blood sugare • dehydration • Low numbers of Electrolytes in the blood, which may cause muscle cramps; weakness, swelling, seizures, coma • Calcium deficiency • blood in urine • Coughing up blood • Hair loss • Hemoptysis • High blood pressure • Swelling in the abdomen • altered taste • Joint pain • Weight gain • swelling of your lower legs or hands • Yeast infection • Low white blood cell count, which may make you more prone to infection • Flushing (skin)	• Eye symptoms including: inflamed eyelids, cataracts, red spot in eye, eye irritation, eye pain, dry eye, excess tearing, pink eye, inflammation and ulceration of the cornea, impairment or loss of vision, high pressure inside eye, bleeding/bruising inside eye • Inflammatory bowel disease • Dry mouth/throat • indigestion • Hemorrhoids • Narrowing of the throat (feeling like you have food stuck in your throat) • Mouth pain and soreness • difficulty speaking • Chills • Pancreatitis • Jaundice • inflammation (swelling and redness) in the bile duct • Lung infection/pneumonia • Fever caused by low white blood cell count • Dizziness • Sleepiness • Anxiety • Insomnia • a burning or prickling sensation that is usually felt in the hands, arms, legs, or feet • Peripheral neuropathy a result of damage to the nerves located outside of the brain and spinal cord (peripheral nerves), often causes weakness, numbness and pain, usually in the hands and feet. • Swollen kidney • a sudden or chronic inability to completely empty the bladder of urine

APPENDIX III – SIDE EFFECTS OF STANDARD OF CARE TREATMENT

The conditioning regimen and drugs used before and after the transplant will result in side effects. There are also risks with the transplant procedure. There is a risk of having all, some, or none of these side effects and the side effects may vary in severity. The severity may be mild, moderate or severe, including death. Any symptoms or conditions that you have before treatment starts may get worse. Also, there is always the chance of a side effect that is not yet known.

Drugs can be given to prevent or lessen the side effects. Many side effects are reversible and go away shortly after the treatment is completed, but in some cases side effects can be serious, long-lasting, or even fatal.

Risks Associated with Pre-Transplant Conditioning With Total Body Irradiation (for participants receiving TBI):

Total Body Irradiation		
Common occurs in more than 20% of patients	**Less Common** occurs in 5 to 20% of patients	**Rare** occurs in fewer than 5% of patients
• nausea and vomiting • diarrhea • cataracts • sterility (inability to have children) • hormone imbalance due to damage to the endocrine gland • stunned growth in children • stomach cramps • mucositis (mouth sores)	• parotitis (swelling and inflammation of the salivary gland) • interstitial pneumonitis (explained below in the damage to vital organs section) • mild reddening of the skin • veno-occlusive disease (VOD - explained below in the damage to vital organs section)	• difficulty swallowing • deformities of the backbone • kidney damage or disease • risk of 2nd cancer years later (when given along with chemotherapy)

Risks associated with Pre-Transplant Conditioning with busulfan/fludarabine (applies only to participants not receiving TBI):

Busulfan		
Common occurs in more than 20% of patients	**Less Common** occurs in 5 to 20% of patients	**Rare** occurs in fewer than 5% of patients
• low white blood cell count with increased risk of	• tiredness (fatigue) • sores in mouth or on lips	• abnormal blood tests results which suggest that

Busulfan		
Common occurs in more than 20% of patients	**Less Common** occurs in 5 to 20% of patients	**Rare** occurs in fewer than 5% of patients
infection ● low platelet count with increased risk of bleeding ● low red blood cell count (anemia) which may cause tiredness, headache, dizziness ● hair loss or thinning, including face and body hair (usually grows back after treatment) ● long-term or short-term infertility (inability to have children) in men and women	• fever • nausea • vomiting • rash • loss of appetite • diarrhea • serious infection due to low white blood cell count	the drug is affecting the liver ● allergic reaction with hives, itching, headache, coughing, shortness of breath, or swelling of the face, tongue, or throat ● scarring of lung tissue, with cough, difficulty breathing, and shortness of breath that may occur after prolonged use, or even months or years after stopping the drug ● secondary cancers ● darkened skin ● heart problems with high-dose treatment, most often in people with thalassemia or others with iron overload ● hormone deficiency ● death due lung damage, bone marrow failure, or other causes

Fludarabine		
Common	**Less Common**	**Rare**
● severe suppression of blood counts ● diarrhea ● anorexia ● mucositis ● nausea/vomiting ● stomatitis ● osteoporosis ● dysuria	● chills ● fever ● GI bleeding ● peripheral edema	● neurotoxicity - agitation and confusion - blurred vision - peripheral neuropathy - hearing loss - headache - cerebellar syndrome - blindness - coma - weakness

Fludarabine		
Common	**Less Common**	**Rare**
		• depression • insomnia • hemorrhagic cystitis (except in FA) • abnormal renal function test • autoimmune hemolytic anemia • deep venous thrombosis • aneurysms • pruritic skin rash • abnormal liver function/liver failure • constipation • transient ischemic attack • dysphagia • myalgia • arthralgia • renal failure

Risks associated with the drugs given to reduce the risk of GVHD (all participants):

Cyclophosphamide		
Common occurs in more than 20% of patients	**Less Common** occurs in 5 to 20% of patients	**Rare** occurs in fewer than 5% of patients
• low white blood cell count with increased risk of infection • hair loss or thinning, including face and body hair (usually grows back after treatment) • nausea • vomiting • loss of appetite • sores in mouth or on lips • bleeding from bladder, with blood in urine • diarrhea • long-term or short-term inability to have children in women and men	• low platelet count (mild) with increased risk of bleeding • darkening of nail beds • acne • tiredness • infection • fetal changes if pregnancy occurs while taking cyclophosphamide	• heart problems with high doses, with chest pain, shortness of breath, or swollen feet • severe allergic reactions • skin rash • scarring of bladder • kidney damage which can lead to kidney failure • heart damage, with trouble getting your breath, swelling of feet, rapid weight gain • scarring of lung tissue, with cough and shortness of breath • second cancer, which can happen years after taking this drug • death from infection, bleeding, heart failure, allergic reaction, or other causes

A drug called Mesna will be given with cyclophosphamide to reduce the risk of damage to the bladder. The most common risks of Mesna include: nausea, vomiting, tiredness, headache, pains in your legs and arms and an unpleasant taste in your mouth.

Sirolimus		
common (occuring in 30 or more out of every 100 persons)	**less common** (occuring in fewer than 30 but more than 5 out of 100 persons)	**rare, but may be serious** (occuring in 5 or fewer out of 100 persons)
• chest pain, feeling weak or tired • pale skin, easy bruising or bleeding, weakness • fever, chills, body aches, flu symptoms • night sweats, weight loss • swelling of face, stomach, hands or feet • pain or burning when urinating • slow healing of a wound • joint pain	• fast heart rate • coughing up blood or mucus • rapid weight gain	▪ pain when breathing, feeling short of breath ▪ feeling like you might pass out ▪ Increased susceptibility to infection ▪ lymphoma and other cancers may result from immunosuppression

Sirolimus		
common (occuring in 30 or more out of every 100 persons)	**less common** (occuring in fewer than 30 but more than 5 out of 100 persons)	**rare, but may be serious** (occuring in 5 or fewer out of 100 persons)
• nausea, vomiting, diarrhea, constipation, stomach pain • headache • acne or skin rash • high triglycerides and cholesterol		

Common side effects of the Eye drops:

Prednisolone acetate ophthalmic solution	**Brimonidine tartrate**
• Blindness (<1% risk of this occurring) • blurred vision • burning, dry, itching eyes • change in vision • decreased vision • difficulty in focusing • drooping of the upper eyelids • eye discharge, excessive tearing • feeling of having something in the eye • redness, irritation, pain, swelling of the eye, eyelid, or inner lining of the eyelid • sensitivity of the eye to light • slow wound healing	• Eye discomfort/itching/redness/burning/stinging, feeling like something is in your eye, • blurred vision, • redness of the eye or eyelid, • swollen or puffy eyes, • sensitivity to light, • nausea, • upset stomach, • headache, • dizziness, • muscle pain, • dry nose or mouth, • drowsiness, • tiredness, • sleep problems (insomnia), or • unusual or unpleasant taste in your mouth.

Risks Associated with Transplantation:

Graft versus Host Disease (GVHD): GVHD can occur either within the first 3 months after the transplant (acute GVHD) or later, usually around 6 to 8 months after the transplant (chronic GVHD).

Acute GVHD commonly involves the skin, liver, and the intestines with symptoms such as a skin rash, jaundice (yellowing of the skin), nausea, vomiting and diarrhea. The treatment of acute GVHD may require high doses of cortisone-like drugs (methylprednisolone or prednisone)

Chronic GVHD usually involves the skin, liver, eyes, glands and joints with symptoms such as skin rash, jaundice (yellowing of the skin), dry mouth or/eyes, weakness or a pain and tightening

around the joints. Chronic GVHD may be mild and respond to drugs which suppress the immune system, or it could be very severe; it may also last for several years.

If GVHD occurs, standard GVHD therapy will be given.

Radiation: As part of this study you may undergo a chest CT to look for infection in your lungs prior to transplant. This procedure involves exposure to ionizing radiation. The average amount of radiation that the average person would receive from this procedure is approximately three times that received from natural sources of radiation by a Minnesota resident in one year (3 mSv). This exposure involves minimal risk and is necessary to obtain the research information desired from participation in this study.

Donor Cell Infusion Reaction: The donor cells are given in a manner similar to a blood transfusion, and there is a small risk of an allergic reaction to the cells as they are given. This may include changes in heart rate or rhythm, changes in blood pressure, fever, chills, sweats, nausea/vomiting, diarrhea, abdominal cramping, and headache. Drugs are given before the cell infusion to reduce the risk of an allergic reaction. If symptoms develop during the infusion, the rate of the infusion may be slowed or stopped and/or additional medications given to reduce the intensity of any reactions.

Marrow Aplasia (Suppression of the Bone Marrow): All patients will have low blood counts from the conditioning, but are expected to recover within a few weeks after the transplant. A drug called filgrastim (G-CSF) may be given to help speed the recovery of the blood counts.

filgrastim (G-CSF)		
Common	**Less Common**	**Rare, but may be serious**
• bone or muscle pain • higher levels of liver enzymes and uric acid in the blood • headache • tiredness	• injection site reaction (redness, pain, or swelling) • nausea	• allergic reaction • spleen enlargement or rupture – symptoms of an enlarged spleen include a feeling discomfort, fullness, or pain on the upper left side of the abdomen; this pain may spread to the left shoulder • serious lung problems (ARDS) • worsening of skin rashes

Marrow aplasia and failure to engraft are names used to describe when blood counts do not recover as expected.

Symptoms of marrow aplasia include increased risk of bleeding and/or bruising due to low platelets, increased risk of infection due to low white blood cell count, and shortness of breath and tiredness as a result of anemia due to low red blood cell count. Marrow aplasia is treated with blood transfusions and growth factor (which stimulates bone marrow cells), and other precautions. Severe or prolonged aplasia (lasting more than 1 month) can lead to death, usually from infection. If the bone marrow does not recover, sometimes it can be corrected by another stem cell transplant; however not all patients are able to have a transplant.

Damage to the Vital Organs: Some patients will experience severe lung problems due to infections such as cyomegalovirus (CMV) and/or a reaction of the lungs to the conditioning. Although treatments are available for this type of pneumonia, interstitial pneumonia can be fatal.

Some patients will suffer veno-occlusive disease of the liver (VOD), a complication that may result from high doses of chemotherapy and/or radiation. Patients who have VOD become jaundiced (yellowish skin), have liver function abnormalities, abdominal swelling, and abdominal pain. Although many patients recover, these complications may result in organ failure and permanent damage, or even death.

Serious Infections: Complete recovery of the immune system may take many months following the initial recovery of the white cell count. During this time, there is an increased risk of infections. Medications to reduce the risk of developing an infection are prescribed during this time; however, preventative treatments are not always effective. If an infection develops, discharge from the hospital may be delayed or re-hospitalization required. Infections can be fatal.

Sterility and Future Childbearing Potential for Men and Women: Radiation and chemotherapy may affect fertility. Male patients may become sterile (unable to produce sperm). Female patients may find that their menstrual cycle becomes irregular or stops permanently. Damage to reproductive tissue may result in birth defects or permanent inability to father a child or become pregnant. These risks and options will be discussed in detail with the medical staff before beginning treatment. However, PREGANCY CAN OCCUR, and an effective method of birth control must be used by sexually active men and women.

Risk to the Fetus: The treatments are NOT safe at any stage of pregnancy. Therefore, pregnant and nursing women are not eligible for this treatment. Women who have the potential of becoming pregnant must use some form of effective birth control.