Valacyclovir Vs. Valganciclovir For After Transplant EBV/CMV Prophylaxis

ADULT CONSENT FORM

You are invited to participate in a research study to compare the effectiveness of valacyclovir to the routinely prescribed valganciclovir in the prevention of certain viral infections (cytomegalovirus/CMV and Epstein-Barr virus/EBV) that cause illness and even death after transplant. You were selected as a possible participant because you have been approved to undergo kidney transplantation. We ask that you read this form and ask any questions you may have before agreeing to be in the study.

This study is being conducted at the University of Minnesota Masonic Children's Hospital by Dr. Priya Verghese, a medical kidney transplant specialist and Dr. Henry Balfour, a virology expert. This study is being supported using internal funding at the University of Minnesota. A description of this clinical trial will be available on http://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 anytime.

STUDY PURPOSE

The purpose of this study is to find a safe and effective way to decrease the risk of two herpes viral infections (CMV and EBV) after kidney transplant. CMV is a common cause of disease after kidney transplants and although treatments are available that make illness due to CMV less common, it still occurs and can be life threatening. EBV is also a cause of disease after transplant and has been linked with after transplant lymphoproliferative disease (PTLD) which is where the patient's white blood cells start to multiply and this can progress to cancer. Currently CMV is prevented by valganciclovir after transplant which is a very expensive medication with many side effects including lowering the white blood cell count. We believe that valacyclovir is a safer and less expensive medication which will not only be as effective as valganciclovir in preventing CMV but may also be able to prevent EBV after transplant. Therefore the purpose of this study is to compare the effectiveness and safety of valacyclovir to valganciclovir in preventing EBV and CMV.

While CMV infection is known to occur despite valganciclovir prophylaxis, its anti-CMV effect is well established in kidney transplant recipients unlike valacyclovir. Therefore you must be aware that you are at risk of mild-severe organ dysfunction related to CMV in the blood or CMV disease.

NUMBER OF PEOPLE TAKING PART IN THE STUDY

We plan to enroll up to 200 pediatric and adult subjects at the University of Minnesota.

STUDY PROCEDURES

If you agree to be in the study you will randomly, like a coin flip, be assigned to receive valacyclovir 500 mg, 1000mg or 1500mg twice a day or valganciclovir 450mg every other day, 450mg once a day or 900 mg once a day by mouth for at least three to six months. The dosage of valacyclovir or valganciclovir you receive is based on your level of kidney function. The decision of whether you will receive valacyclovir or valganciclovir is random and will be determined when you consent to be in the study. Once you begin taking the valacyclovir or valganciclovir we will contact you to review your daily dosing as well as any new medications

you take and any adverse events you experience, weekly for the first month after your transplant and then monthly until dosing is complete. If you have a scheduled clinic visit during these times study staff will meet with you then. If you do not have a clinic visit scheduled you can choose whether you would like study staff to contact you by phone or email to review medication dosing. We will collect left-over blood from your samples at the laboratory and test them to look for the presence and amount of CMV and EBV in your body. In addition, we will test your blood for antibodies to CMV and EBV twice a year. If you do not have a clinical blood draw done at least once a month, we may ask you to undergo a blood draw for our research study and will collect 2-3 teaspoons of blood.

At the time of any biopsies of your kidney that might occur in the first year after transplant, we will take two to three cores of kidney tissue for research analysis purposes, provided your clinical team has sufficient tissue to spare. We will not have them do another needle stick into your kidney for our study and will only use extra tissue provided by your team. This tissue will be studied for the presence of EBV or CMV in the kidney tissue.

STORED SERUM PLASMA AND KIDNEY TISSUE SAMPLES

At the same time that routine blood samples are drawn for lab tests (viral testing and drug safety assessment labs), we will also draw and store samples of serum and plasma to be frozen and stored for future studies related to kidney transplant donors. Your kidney biopsy tissue will also be frozen and stored. These stored samples will be coded with identifiers that cannot be directly linked to you. The samples would be destroyed at your request. The storage of your samples is optional. You can select the appropriate check box at the end of this form to note your preference. Stored blood samples will be used for further viral testing or drug level assessment based on preliminary results and will be discarded after 40 years.

RISKS OF PARTICIPATION

The blood draw may cause some minor discomfort and/or bruising. The risk of infection is very low because of the use of sterile technique but we will use extra blood at the laboratory and will have you undergo a blood draw only if you do not have clinical blood draws done at least monthly. The risks of the kidney biopsy will not be increased by our research since we will only be taking an extra piece of tissue that is provided to us by your physician performing the biopsy.

RISKS OF SIDE EFFECTS

Val**g**anciclovir is considered to be standard of care after transplant for the prevention and treatment of CMV infection and disease after transplant. When administered to transplant recipients who are immunosuppressed on multiple medications, common adverse events and laboratory abnormalities include diarrhea, fever, nausea, tremor, leukopenia (low white blood cell count), anemia (low red cell count), low platelet count and vomiting. In a clinical study for the treatment of CMV retinitis in HIV-infected patients, the common adverse events reported by patients receiving this drug included diarrhea (16%), nausea (8%), headache (9%), leukopenia (11%) and anemia (8%). There is a black box warning on the package insert of valganciclovir as below for hematologic toxicity, carcinogenicity (increased chance for cancer), teratogenicity (increased chance of abnormalities to babies born to mothers taking the drug) and impairment of fertility (increased difficulty for people taking the drug to have offspring or babies). Although many of these side effects have never been demonstrated in humans, we want you to be aware.

WARNING: HEMATOLOGIC TOXICITY, CARCINOGENICITY, TERATOGENICITY, AND IMPAIRMENT OF FERTILITY

- Clinical toxicity of Valcyte, which is metabolized to ganciclovir, includes granulocytopenia, anemia, and thrombocytopenia.
- In animal studies, ganciclovir was carcinogenic, teratogenic, and caused aspermatogenesis

The common side effects of valacyclovir include rash (8%), abdominal pain (1% to 11%), nausea (5% to 15%), vomiting (less than 1% to 6%), headache (13% to 38%) and fatigue (8%).

BENEFITS OF PARTICIPATION

There may be no potential benefit to participation for subjects who received the standard of care valganciclovir**.**

ALTERNATIVES TO PARTICIPATION

The alternative to joining this study is not to participate. If you chose not to participate you will receive standard of care valganciclovir as CMV prophylaxis during the first six months after your kidney transplant. You may decline to participate, or withdraw participation once the study has begun, without limiting your ability to receive future care from the University of Minnesota Medical Center, Fairview. If the study staff decides it is in your best interest, or if you significantly fail to follow the study requirements, your participation in this study may be ended without your permission.

CONFIDENTIAL NATURE OF THE STUDY

The records of this study will be kept private. In any publications or presentations, we will not include any information that will make it possible to identify you as a subject. Your record for the study may, however, be reviewed by regulatory authorities including the FDA, study monitor, auditors, and by departments at the University with appropriate regulatory oversight. Your information may also be transmitted and/or reviewed by University of Minnesota (UM), University of Minnesota Physicians (UMP) and University of Minnesota Medical Center, Fairview personnel who monitor research and UM, UMP and Medical Center personnel who need access to the information to complete the clinical study. These organizations and people must keep the information private as required by law. To these extents, confidentiality is not absolute.

STUDY COSTS/COMPENSATION

There is no charge to you or your insurance company for study visits, tests, or procedures directly related to this study. The costs of your standard medical care will be billed to you and/or your insurance company in the usual manner. The costs of the valacyclovir or valganciclovir will be billed to your health insurance company, and you will be responsible for paying any deductibles, copayments or coinsurance that are a normal part of your health insurance plan. If you do not have health insurance, you will be responsible for those costs. Before you agree to be in this study,

you may want to contact your healthcare payer/insurer to see if the cost of the medication will be covered by your plan. ☐ ☐

RESEARCH RELATED INJURY

In the event 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.

PROTECTED HEALTH INFORMATION (PHI)

Your PHI created or received for the purposes of this study is protected under the federal regulation known as HIPAA. Please refer to the attached HIPAA authorization for details concerning the use of this information.

VOLUNTARY NATURE OF THE STUDY

Participation in this study is voluntary. Your decision whether or not to participate in this study will not affect your current or future relations with your doctor, the University of Minnesota Masonic Children's Hospital or University of Minnesota Medical Center, Fairview. If you decide to participate, you are free to withdraw at any time without affecting those relationships.

If any findings arise during the study which could affect your health and which might influence your treatment, you and your doctor will be informed immediately so that medical treatment can be started. Likewise, any results of the study which might affect your willingness to participate in this study will be shared with you.

CONTACTS AND QUESTIONS

The researchers conducting this study are Dr. Priya Verghese and Dr. Henry H Balfour Jr. You may ask any questions you have now. If you have questions or concerns regarding the study and would like to talk later about the research and research subjects' rights or wish to report a research-related injury, please contact Dr. Verghese at 612-626-2922.

If you have any questions or concerns regarding the study and would like to talk to someone other than the researcher(s), contact the Fairview Research Helpline at telephone number 612-672-7692 or toll free at 866-508-6961. You may also contact this office in writing or in person at Fairview Research Administration, 2433 Energy Park Drive, St Paul, MN 55108.

You will be given a copy of this form to keep. You are making a decision whether or not to participate in this study. Please read the questions in the box below and answer your preference. You may feel free to answer yes or no to any or all of questions without affecting your eligibility for our study.

You agree to the storage of your plasma, serum and kidney tissue.	YES NO

We are requesting your permission to contact you in the future when there are studies which have been approved by our Human Research Subjects Protection Program (RSPP) and which may be of interest to you. I give you permission to contact me for future RSPP approved studies of potential interest to me.	YES ☐ NO ☐

Your signature below indicates that you have read the information in this consent form and have decided to participate in this study. You may withdraw at any time without prejudice after signing this form should you choose to discontinue participation in this study.

Signature of Subject:_____Date/Time: _____

Print Name: _____

Signature of Legally Authorized Representative (LAR) (if needed): _____

Date/Time: _____

Print Name of LAR: _____

Signature of Person Obtaining Consent:_____Date/Time: _____

Print Name: _____

Valacyclovir Vs. Valganciclovir For After Transplant EBV/CMV Prophylaxis

PARENT CONSENT FORM

Your child is invited to participate in a research study to compare the effectiveness of valacyclovir to the routinely prescribed valganciclovir in the prevention of certain viral infections (cytomegalovirus/CMV and Epstein-Barr virus/EBV) that cause illness and even death after transplant. Your child was selected as a possible participant because he/she has been approved to undergo kidney transplantation. We ask that you read this form and ask any questions you may have before agreeing to be in the study.

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STUDY PURPOSE

The purpose of this study is to find a safe and effective way to decrease the risk of two herpes viral infections (CMV and EBV) after kidney transplant. CMV is a common cause of disease after kidney transplants and although treatments are available that make illness due to CMV less common, it still occurs and can be life threatening. EBV is also a cause of disease after transplant and has been linked with after transplant lymphoproliferative disease (PTLD) which is where the patient's white blood cells start to multiply and this can progress to cancer. Currently CMV is prevented by valganciclovir after transplant, which is a very expensive medication with many side effects including, lowering the white blood cell count. We believe that valacyclovir is a safer and less expensive medication which will not only be as effective as valganciclovir in preventing CMV but may also be able to prevent EBV after transplant. Therefore the purpose of this study is to compare the effectiveness and safety of valacyclovir to valganciclovir in preventing EBV and CMV.

While CMV infection is known to occur despite valganciclovir prophylaxis, its anti-CMV effect is well established in kidney transplant recipients unlike valacyclovir. Therefore you must be aware that your child is at risk of mild-severe organ dysfunction related to CMV in the blood or CMV disease.

NUMBER OF PEOPLE TAKING PART IN THE STUDY

We plan to enroll up to 200 pediatric and adult subjects at the University of Minnesota.

PROCEDURES FOR THE STUDY

If you agree for your child to be in the study, your child will experience the following:

Your child will randomly, like a coin flip, be assigned to receive valacyclovir or valganciclovir by mouth for three to twelve months. The dosage of valacyclovir or valganciclovir your child receives is based on his/her weight and level of kidney function. The decision of whether your child will receive valacyclovir or valganciclovir is random and will be determined when you and your child consent to be in the study. Once your child begins taking the valacyclovir or valganciclovir we will contact you to document your child's daily dosing as well as any new medications your child takes and any adverse events he/she

experiences, weekly for the first month after your child's transplant and then monthly until dosing is complete. If your child has a scheduled clinic visit during these times study staff will meet with you/your child then. If your child does not have a clinic visit scheduled you/your child can choose whether you would like study staff to contact you by phone or email to review you/your child's daily dosing. We will collect left-over blood from your child's samples at the laboratory and test them to look for the presence and amount of CMV and EBV in your child's body. In addition, we will test your child's blood for antibodies to CMV and EBV twice a year. If your child does not have a clinical blood draw done at least once a month, we may ask your child to undergo a blood draw for our research study and will collect 1-3 teaspoons of blood.

If your child undergoes any biopsies in the first year after transplant, we will take two to three cores of kidney tissue for research analysis purposes, provided your clinical team has sufficient tissue to spare. We will not have them do another needle stick into your child's kidney for our study and will only use extra tissue provided by your child's team. This tissue will be studied for the presence of EBV or CMV in the kidney tissue.

STORED SERUM PLASMA AND KIDNEY TISSUE SAMPLES

At the same time that routine blood samples are drawn for lab tests (viral testing and drug safety assessment labs), we will also draw and store samples of serum and plasma to be frozen and stored for future studies related to kidney transplant donors. Your child's kidney biopsy tissue will also be frozen and stored. These stored samples will be coded with identifiers that cannot be directly linked to your child. The samples would be destroyed at your/your child's request. The storage of your child's samples is optional. You can select the appropriate check box at the end of this form to note your preference. Stored blood samples will be used for further viral testing or drug level assessment based on preliminary results and will be discarded after 40 years.

RISKS OF TAKING PART IN THE STUDY

The blood draw may cause some minor discomfort and/or bruising. The risk of infection is very low because of the use of sterile technique. The risks of the kidney biopsy will not be increased by our research since we will only be taking an extra piece of tissue that is provided to us by your child's physician performing the biopsy.

RISKS OF SIDE EFFECTS

Valganciclovir is considered to be standard of care after transplant for the prevention and treatment of CMV infection and disease after transplant. When administered to transplant recipients who are immunosuppressed on multiple medications, common adverse events and laboratory abnormalities include diarrhea, fever, nausea, tremor, leukopenia (low white blood cell count), anemia (low red cell count), low platelet count and vomiting. In a clinical study for the treatment of CMV retinitis in HIV-infected patients, the common adverse events reported by patients receiving this drug included diarrhea (16%), nausea (8%), headache (9%), leukopenia (11%) and anemia (8%). There is a black box warning on the package insert of valganciclovir as below for hematologic toxicity, carcinogenicity (increased chance for cancer), teratogenicity (increased chance of abnormalities to babies born to mothers taking the drug) and impairment of fertility (increased difficulty for people taking the drug to have offspring or babies). Although many of these side effects have never been demonstrated in humans, we want you to be aware.

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The common side effects of valacyclovir include rash (8%), abdominal pain (1% to 11%), nausea (5% to 15%), vomiting (less than 1% to 6%), headache (13% to 38%) and fatigue (8%).

BENEFITS OF TAKING PART IN THE STUDY

There may be no potential benefit to participation for subjects who received the standard of care valganciclovir. The side effect profile for valacyclovir is less than that of the current standard of care medication (valganciclovir). Therefore, if your child is assigned into the arm of the group that receives valacyclovir your child will most likely have less leukopenia (low white blood cell count). This means that there is less chance that your child's antiviral prophylaxis will need to be dose reduced. It also means that your child's immunosuppression doses may not need to be reduced because of a low white blood cell count thereby leading to less rejection.

ALTERNATIVES TO TAKING PART IN THE STUDY

The alternative to joining this study is not to participate. If you chose not to participate your child will receive standard of care valganciclovir as CMV prophylaxis after his/her kidney transplant. You may decline to participate, or withdraw participation once the study has begun, without limiting your child's ability to receive future care from the University of Minnesota Medical Center, Fairview. If the study staff decides it is in your child's best interest, or if you/your child significantly fail to follow the study requirements, your child's participation in this study may be ended without your/your child's permission.

CONFIDENTIAL NATURE OF THE STUDY

The records of this study will be kept private. In any publications or presentations, we will not include any information that will make it possible to identify you as a subject. Your record for the study may, however, be reviewed by regulatory authorities including the FDA, study monitor, auditors, and by departments at the University with appropriate regulatory oversight. Your information may also be transmitted and/or reviewed by University of Minnesota (UM), University of Minnesota Physicians (UMP) and University of Minnesota Medical Center, Fairview personnel who monitor research and UM, UMP and Medical Center personnel who need access to the information to complete the clinical study. These organizations and people must keep the information private as required by law. To these extents, confidentiality is not absolute.

STUDY COSTS/COMPENSATION

There is no charge to you or your insurance company for study visits, tests, or procedures directly related to this study. The costs of your child's standard medical care will be billed to you and/or your insurance company in the usual manner. The costs of the valacyclovir or valganciclovir will be billed to your health insurance company, and you will be responsible for paying any deductibles, copayments or coinsurance that are a normal part of your health insurance plan. If you do not have health insurance, you will be responsible for those costs. Before you agree to be in this study, you may want to contact your healthcare payer/insurer to see if the cost of the medication will be covered by your plan.

RESEARCH RELATED INJURY

In the event 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 your child has suffered a research related injury let the study physicians know right away.

VOLUNTARY NATURE OF THE STUDY

Participation in this study is voluntary. Your decision whether or not to participate in this study will not affect your child's current or future relations with your child's doctor, the University of Minnesota Masonic Children's Hospital or University of Minnesota Medical Center, Fairview. If your child decides to participate, your child is free to withdraw at any time without affecting those relationships.

If any findings arise during the study which could affect your child's health and which might influence his/her treatment, you and your child's doctor will be informed immediately so that medical treatment can be started. Likewise, any results of the study which might affect your/your child's willingness to participate in this study will be shared with you.

PROTECTED HEALTH INFORMATION (PHI)

Your child's PHI created or received for the purposes of this study is protected under the federal regulation known as HIPAA. Please refer to the attached HIPAA authorization for details concerning the use of this information.

CONTACTS AND QUESTIONS

The researchers conducting this study are Dr. Priya Verghese and Dr. Henry H Balfour Jr. You may ask any questions you have now. If you have questions or concerns regarding the study and would like to talk later about the research and research subjects' rights or wish to report a research related injury, please contact Dr. Verghese at 612-626-2922.

To share feedback privately about your research experience, including any concerns about the study, call the Research Participants Advocate Line: 612-625-1650 or give feedback online at www.irb.umn.edu/report.html. You may also contact the Human Research Protection Program in writing at D528 Mayo, 420 Delaware St. Southeast, Minneapolis, Minnesota 55455.

You will be given a copy of this form to keep. You are making a decision whether or not to allow your child to participate in this study. Please read the questions in the box below and answer your preference. You may feel free to answer yes or no to any or all of questions without affecting your child's eligibility for our study.

You agree to the storage of your child's plasma, serum and kidney tissue.	YES ☐ NO ☐
We are requesting your permission to contact you in the future when there are studies which have been approved by our Human Research Subjects Protection Program (RSPP) and which may be of interest to you/your child. I give you permission to contact me for future RSPP approved studies of potential interest to me/my child.	YES ☐ NO ☐

STATEMENT OF CONSENT
I have read the above information. I have had the opportunity to ask questions, and my questions have been answered. I agree to enroll my child in this study.

If your child turns 18 years old while in this study, s/he will be asked for his/her permission to continue in the study and will be required to sign a consent as an adult at that time.

You will receive a copy of this form. A copy of the study protocol is available upon request.

PATIENT NAME _____

_____ _____ _____
Signature of Parent or Legal Representative Date Time

_____
Printed Name of Parent or Legal Representative

_____ _____ _____
Signature of Person Obtaining Consent Date Time

_____
Printed Name of Person Obtaining Consent

Was an interpreter utilized to obtain consent? ☐ YES ☐ NO

Was a translated Short Form used? ☐ YES ☐ NO

_____ _____
Signature of Interpreter (if applicable) Date