VALACYCLOVIR VERSUS VALGANCICLOVIR FOR POST-TRANSPLANT CYTOMEGALOVIRUS/EPSTEIN-BARR VIRUS PROPHYLAXIS: A RANDOMIZED CONTROLLED TRIAL

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List of Abbreviations

AE	Adverse Event
BID	twice daily
BMP	basic metabolic panel
CBC	complete blood count
CFR	Code of Federal Regulations
CMV	cytomegalovirus
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
DSMP	Data and Safety Monitoring Plan
EBV	Epstein-Barr virus
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICH	International Conference on Harmonization
IDS	Investigational Drug Services
IRB	Institutional Review Board
KTx	kidney transplant
PCR	Polymerase Chain Reaction
PHI	Protected Health Information
SAE	Serious Adverse Event
QD	once daily
QOD	every other day
valA	valAcyclovir
valG	valGanciclovir

Study Summary

Title	**Valacyclovir versus Valganciclovir for Post-transplant Cytomegalovirus/Epstein-Barr Virus Prophylaxis: A Randomized Controlled Trial**
Short Title	ValA vs ValG for Post-transplant CMV/EBV Prevention
Protocol Number	11.0
Phase	Pilot
Methodology	Randomized Control Trial
Study Duration	36 months
Study Center(s)	Single-Center
Objectives	To compare the effectiveness of valacyclovir (valA) to valganciclovir (valG) in the prevention of EBV and CMV viremia post-kidney transplant.
Number of Subjects	Total of 200
Diagnosis and Main Inclusion Criteria	Adult and pediatric kidney transplant recipients
Study Product, Dose, Route, Regimen	Valacyclovir Dose: 500-1500mg bid Oral
Duration of administration	3-12 months dependent on treatment assignment and donor and recipient viral serostatus in accordance with standard of care.
Reference therapy	Valganciclovir Oral
Statistical Methodology	Incidence of viremia will be compared using a two-sided Fisher exact test and viral load-time curve areas will be compared using a Mann-Whitney test. A p-value of $\leq$0.05 will be considered significant.

1 Introduction

Infections are now a leading cause of death and morbidity in kidney transplant recipients. Herpes viruses such as Epstein-Barr virus (EBV) and cytomegalovirus (CMV) are particularly troublesome.

At the present time, valganciclovir (valG) is the primary prophylactic agent against CMV in kidney transplant (KTx) recipients. Although many centers try to prevent CMV disease by placing all or in some centers, only the high risk patients (defined as CMV antibody negative patients receiving organs from CMV antibody positive donors) on antiviral prophylaxis with valG for three to 12 months post-KTx, there continue to be patients with break-through infections. CMV viremia has been noted in 22% of pediatric post-KTx recipients, and the incidence at the University of Minnesota (UMMC) in all KTx recipients is as high as 17% despite valG prophylaxis. CMV disease post-KTx can manifest as fever, leucopenia, or mild to severe organ involvement. While an effective anti-CMV drug, valG has a number of adverse effects including leucopenia, also a side effect of mycophenolate mofetil (MMF), one of the cornerstones of current anti-rejection regimens. Combined therapy with MMF and valG frequently results in leucopenia associated infection or leucopenia necessitating reduction in MMF doses, increasing the risk of rejection. In addition, valG is prohibitively expensive. Therefore, rather than prophylaxis, many centers adopt a pre-emptive therapeutic approach whereby post-Ktx patients are screened for CMV, and at new onset viremia, valG is initiated. This approach has been associated with increased CMV infections and resistant viral strains.

Therefore, there is need for an alternate drug with a more benign side effect profile and equal effectiveness against CMV. Valacyclovir (valA) was shown to reduce the incidence and delay the onset of CMV disease in both CMV seronegative patients ($P<0.001$) and CMV seropositive patients ($P=0.03$) and has fewer severe adverse events. In fact, very high doses of valA (8g/day), for post-KTx CMV prophylaxis were shown to have no severe or treatment-limiting side effects compared to placebo.

Currently, prevention of EBV infection is conducted by close monitoring of patients and immunosuppression reduction at the discovery of EBV viremia. A recent study suggested that valG prophylaxis post-KTx is protective against EBV infection, but it had design flaws and the number of subjects was limited. Therefore to date, the anti-EBV effect of valG is poorly defined. EBV can present post-KTx as infectious mononucleosis syndrome, hepatitis and, most importantly, can initiate potentially fatal lymphoproliferative disorders (PTLD). Between October 2003 and December 2009, EBV viremia occurred in 20% of adults and 50% of pediatric KTx recipients (60/120) at UMMC, and, PTLD occurred in 6% (7/120) of pediatric recipients. Effective anti-EBV prophylaxis could substantially improve KTx outcomes. ValA therapy resulted in a statistically significant reduction in oral EBV shedding, accompanied by a clinical benefit, and valA is currently used for the therapy of severe cases of infectious mononucleosis in the community.

This document is a protocol for a human research study. This study will be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part

312 or 812 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

Therefore as stated above CMV and EBV remain critical posttransplant complications that can significantly and negatively impact patient and kidney transplant survival. In addition to overt CMV and EBV related issues detailed above, subclinical CMV and/or EBV viremia have been associated with deterioration in kidney function in KTx recipients. The significance of this research also includes the potential for substantial cost-savings. At UMMC, even with discounted pricing due to the University status and bulk ordering, a 90 day supply of 450mg doses of valG administered twice daily is approximately $11,000 compared to $3250 for 1.5g tablets twice daily of valA. At least 200 patients receive kidney transplants each year at UMMC, making the impact of a successful outcome from this research a saving of at least $1.55 million per year in addition to the cost-saving of reducing viral infection or rejection related admissions and expenses.

UMMC conducts surveillance biopsies at 3 and 12 months post-KTx on some adult transplant recipients, providing an ideal opportunity to assess kidney tissue for EBV and CMV via molecular and immunological assays. We think it likely that post-KTx, kidneys exposed to an immunosuppressed milieu allowing viral multiplication will increase the likelihood of isolating the virus from infected recipients; a pivotal step in our understanding of the mechanisms of CMV and EBV infection post-KTx.

In summary, valA is less expensive, with fewer adverse effects, and less likelihood of causing leucopenia than valG. If this agent has equivalent efficacy in CMV and any efficacy in EBV prophylaxis, the use of valA will result in significant financial savings, a reduced risk of leucopenia-associated infection, and a lower incidence of rejection by allowing the use of standard MMF doses.

1.2 Investigational Agent

Valacyclovir (valacyclovir hydrochloride) is the hydrochloride salt of the *L*-valyl ester of the antiviral drug acyclovir. Caplets are for oral administration. Each caplet contains valacyclovir hydrochloride equivalent to 500 mg or 1 gram valacyclovir and the inactive ingredients carnauba wax, colloidal silicon dioxide, crospovidon, FD&C Blue No. 2 Lake, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, povidone, and titanium dioxide. The blue, film-coated caplets are printed with edible white ink.

Valacyclovir oral suspension (25 mg/mL or 50 mg/mL) may be prepared extemporaneously from 500 mg VALTREX Caplets for use in pediatric patients for whom a solid dosage form is not appropriate.

The chemical name of valacyclovir hydrochloride is *L*-valine, 2[(2-amion-1,6-dihydro-6-oxo-*9H*-purin_9_yl)methoxy]ethyl ester, monohydrochloride.

Valacyclovir is a nucleoside analogue DNA polymerase inhibitor. Valacyclovir hydrochloride is rapidly converted to acyclovir which has demonstrated antiviral activity against HSV types 1 (HSV-1) and 2 (HSV-2) and VZV both in cell culture and in vivo. The inhibitory activity of acyclovir is highly selective due to its affinity for the enzyme thymidine kinase (TK) encoded by HSV and VZV. This viral enzyme converts acyclovir into acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes.

Valganciclovir (valganciclovir hydrochloride) contains valganciclovir hydrochloride (valganciclovir HCl), a hydrochloride salt of the L-valyl ester of ganciclovir that exists as a mixture of two diasteromers. Ganciclovir is a synthetic guanine derivative active against CMV.

Tablets are available as 450 mg for oral administration. Each tablet contains 496.3 mg of valganciclovir HCl (corresponding to 450 mg of valganciclovir), and the inactivie ingredients microcrystalline cellulose, povidone K-30, crospovidone and stearic acid. The film-coat applied to the tablets contains Opadry Pink.

For pediatric patients, valganciclovir HCl is available in an oral solution that must be prepared by a pharmacist prior to dispensing. Valganciclovir HCl for oral solution (50 mg per mL) is supplied as a white to slightly yellow powder for constitution, forming a colorless to brownish yellow tutti-frutti flavored solution. Available in glass bottles containing approximately 100 mL of solution after constitution.

Valganciclovir is an L-valyl ester (prodrug) of ganciclovir that exists as a mixture of two disteromers. After oral administration, both diastereomers are rapidly converted to ganciclovir by intestinal and hepatic esterases.

1.3 Previous Clinical Experience

The anti-EBV effect of valG has not been conclusively demonstrated or proven. On the other hand, data from infectious mononucleosis intervention trials document that two weeks of valA therapy resulted in a statistically significant reduction in oral EBV shedding, accompanied by a clinical benefit (1, 2), and valA is currently used for the therapy of severe cases of infectious mononucleosis in the community (1, 3).
Oral acyclovir has been shown to prevent CMV disease in post-KTx recipients (4-7) and valA in particular has been shown to reduce the incidence and delay the onset of CMV disease in both CMV seronegative patients ($P<0.001$) and CMV seropositive patients ($P=0.03$) (8). But since that trial did not include a comparison arm with the current standard of care which is valG and did not provide information on the anti-EBV effect of the valA, our study is critical in proving the effectiveness of valA for CMV and EBV prophylaxis.

*V*alG is associated with adverse events including diarrhea, fever, nausea, vomiting, tremor, leucopenia, neutropenia, anemia and thrombocytopenia in ≥20% of patients based on their package insert which we have attached. ValG induced leucopenia often necessitates a reduction in immunosuppressive therapy, increasing the risk of allograft rejection. Fewer severe adverse events are related to valA, including rash (8%), abdominal pain (1% to 11%), nausea (5% to 15%), vomiting (less than 1% to 6%), headache (13% to 38%) and fatigue (8%). Very high doses of valA (8g/day) for post-KTx CMV prophylaxis was shown to have no severe or treatment-limiting side effects compared to placebo (8).

1.4 Dose Rationale and Risk/Benefits

Prior research at the University of Minnesota has shown that valacyclovir 1g every 8 hours for a total daily dose of 3g is well tolerated and was associated with a reduction in EBV excretion (1) in patients with infectious mononucleosis. Subsequently a study done at the University of Minnesota to characterize the pharmacokinetics and explore the pharmacodynamics of acyclovir in plasma and oral washings of 8 subjects with EBV infectious mononucleosis receiving the same daily dose of valacyclovir (3g) as a twice daily dosing of 1500 mg twice daily demonstrated safety and showed that the quantity of EBV DNA in oral washings and blood, and the severity of illness, measured by a graded scale, decreased during treatment (9).

Therefore in order to increase the likelihood of compliance in our patients, we have decided to utilize 1.5g twice a day dosing of valacyclovir and since it was shown to be effective as therapy in the above study, we hypothesize that it will be adequate for anti-viral prophylaxis as intended in this study. The dose will of course be adjusted based on GFR and in pediatric patients based on their weight as detailed in package insert and below.

No major side effects are anticipated since even very high doses of valA (8g/day), for post-KTx CMV prophylaxis were shown to have no severe or treatment-limiting side effects compared to placebo (10).

2 Study Objectives

Primary Objectives:
To compare the effectiveness of valacyclovir (valA) compared valganciclovir (valG) in the prevention of EBV and CMV viremia post-KTx.

To compare the proportion of patients requiring dose reduction or cessation of valA compared to valG due to adverse drug side effects.

Secondary Objective:
To identify the presence and quantity of EBV and CMV in renal tissue biopsies from kidney transplant recipients.

3 Study Design

This is a single-center, prospective, randomized, pilot study of up to 200 kidney transplant recipients from the University of Minnesota Medical Center. Randomization of subjects will be in a 1:1 ratio to receive either ValA or standard of care regimen of ValG. Duration of therapy will be 3-13 months.

Subjects will be assessed weekly then monthly for medication compliance, as well as assessing adverse events. Subjects will be assessed at their routine clinic visits, or via email/telephone. Subjects will be followed for a total of 12-13 months, or for an additional 30 days after stop of the drug for adverse events.

Blood samples will be collected by using left-over standard of care samples for immunosuppression drug analysis. From these samples, qualitative PCR assay (qPCR) will assess CMV and EBV for up to six months post study drug cessation. Complete blood count and metabolic panels will be collected clinically, and results recorded for this study. CMV and EBV IgG and IgM levels will be measured bi-annually until seroconversion. In the cases where blood is not drawn for clinical purposes at least once a month, 10-15ml of the subject's blood may be collected for this testing for research purposes. Surveillance kidney transplant biopsies are obtained at the time of transplant, 3 months post-transplant, 12 months post-transplant, and as clinically indicated. For the duration of subject study participation, kidney tissue (two to three cores) from any biopsy will be shared with the research team.

Subjects will be followed-up regularly by the research team during the first year post transplant. During these follow-up assessments, the research team will assess drug adherence as well as evaluate side effects. If subjects are seen during a standard of care visit, laboratory values and a review of medical records will also be performed to assess any potential adverse events.

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

- Adult or pediatric kidney transplant recipients
    - Adult cases are defined as patients transplanted and cared for at the University of Minnesota Medical Center, East Bank campus.
    - Pediatric cases are defined as patients transplanted and cared for at the University of Minnesota Masonic Children's Hospital.
- Consent to participate in the study.

4.2 Exclusion Criteria

- Documented allergy to valA or valG

- Recipients that are unable to independently understand the consent form.
- Pregnant

4.3 Early Withdrawal of Subjects from the Study

Subjects may withdraw from the study at any time. If a subject withdraws consent, all follow up will stop, however data collected up to that point will still be used. Subjects may be withdrawn from the study for the following reason:

- Patient chooses to withdraw consent

4.3.1 Early Withdrawal of Subjects from Drug

Subjects may be withdrawn from drug early for the following reasons:

CMV disease requiring therapy with valG. Cytomegalovirus disease will be defined as CMV DNA in the blood (viremia) on two or more occasions with clinical and/or pathological confirmation of CMV end-organ disease.

- PI decides that further treatment in not in the best interest of the subject
- Graft failure
- Pregnancy
- Treatment related anaphylaxis

4.3.2 Data Collection and Follow-up for Withdrawn Subjects

Subjects will be followed for 12-18 months post-transplant procedure. Please refer to Table 1 for data points and frequency.

5 Study Procedures

5.1 Subject Recruitment and Screening

Initial contact regarding the research study will be done by the transplant clinical team or clinical research team once notification of treatment date is set. For potential subjects that are receiving a transplant from a living donor, the study team will approach for informed consent prior to transplant surgery. For subjects that receive a transplant from a deceased donor, because of time constraints, the study team may approach the patient after they are placed on the transplant list to introduce the study. Informed consent will then be obtained up to 7 days post-operatively.

5.2 Randomization

The randomization will be done in a 1:1 fashion and will be computer generated.

5.3 Laboratory Testing

Blood is collected in accordance to standard of care procedures for these patients. Left-over blood from the clinical laboratories of subjects will be obtained and tested for CMV and EBV quantitative PCR assay (qPCR), at minimum weekly for the first month and monthly for the first year to year and a half post-KTx. Acyclovir levels will be measured

at 1 month in patients randomized to valA. CMV and EBV IgG and IgM levels will be measured bi-annually for patients who are seronegative until seroconversion after which they will no longer be checked. Safety labs include complete blood counts and basic metabolic panels which will be done for recipients randomized to valA monthly while participating in the study.

If the labs are not being collected at a minimum of weekly for the first month and then monthly for the first year, the study team will collect 10-15mL of blood from the subjects for research procedures.

Half to one core of kidney tissue will be obtained, if available, from all kidney transplant biopsies performed during the first year post-KTx.

5.4 Schedule of Events

All assessments will be completed during routine clinical visits when feasible. If the participant does not have a scheduled clinic visit, the participant or parent/guardian can choose to receive an email or phone call follow-up of drug adherence and adverse events. Assessments will continue until at least 30 days after last dose of anti-viral.

Visit Schedule	**Pre-KTx**	**KTx**	**Weekly** During Month 1	**Monthly** through End of Study Period
CBC and BMP[1] (routine clinical lab)	X		X	X
CMV PCR, EBV PCR[2] (Balfour research lab)	X		X	X
CMV IgG, EBV IgG & IgM[2] (Balfour research lab)	X			X[3]
Acyclovir levels				X[4]
Kidney bx tissue[5]		X		X[3]
Medication compliance			X	X[6]
Adverse Events assessment			X	X[6]

1 CBCs and BMP are performed routinely in post-transplant patients. If these are not done clinically, we will collect and perform for research safety monitoring
2 PCRs will be run using leftover blood collected clinically. If no leftover blood is available, we will collect a research specimen.

3 Month 6 only
4. Month 1 only if randomized to valA
5. Kidney biopsies are performed routinely during the first year post-transplant. Paraffin-embedded scrolls will be requested from leftover tissue.
6. Completed monthly until 1 month after cessation of the treatment

6 Study Drug

6.1 Description

Valacyclovir is a nucleoside analogue DNA polymerase inhibitor capsule of 500 mg.

Valganciclovir is a cytomegalovirus nucleoside analogue DNA polymerase inhibitor tablet of 450 mg.

6.2 Treatment Regimen

Dosing of valG and valA will be based on level of renal function assessed by glomerular filtration rate (GFR).

Table 2: val**A** (val**A**cyclovir) dosing based on GFR				
GFR	> 50ml/min	30-49ml/min	10-29ml/min	< 10ml/min
Adults	1500mg BID	1000mg BID	500mg BID	500mg QD
Children	20mg/kg BID	15mg/kg BID	7.5mg/kg BID	7.5mg/kg QD

Table 3: val**G** (val**G**anciclovir) dosing based on GFR					
GFR	≥ 60ml/min	40-59ml/min	25-39ml/min	10-24 ml/min	< 10ml/min
Adults	900mg QD	450mg QD	450mg QOD	450 mg twice weekly	Hold dose
Children	7 x BSA x Creatinine Clearance (CrCl) *(calculated by modified Schwartz formula and Cockroft-Gault for less than and equal to 17 years of age respectively; max 900 QD; max CrCl 150 mL/min/1.73 mL/m2)*				Hold dose

6.3 Duration of Therapy

Duration of therapy is dependent on donor and recipient antibody status.

Adult subjects will be treated with their assigned study drug (ValA or ValG) for **three months,** unless the donor is antibody positive and the recipient is antibody negative (D+R-) to CMV/EBV, then patient will get six months of prophylaxis.

Pediatric transplant recipients will be treated for **twelve months except** if both the donor and the recipient are antibody negative **(D- R-)** for both CMV and EBV, subjects will be treated for **three months**.

Patients that are randomized to ValA that develop CMV disease or CMV viremia X2 may discontinue ValA and begin standard of care treatment with ValG. At that time they will continue research related follow up but valA use is up to the discretion of the treating physician. At that time all protocol directed safety follow up with be discontinued; however, outcomes will be followed until month 12.

6.4 Method for Assigning Subjects to Treatment Groups

Subjects will be randomized by the IDS pharmacy in 1:1 fashion using computer allocation to receive either valA or valG, and will notify the study team of the randomization assignment

6.5 Preparation and Administration of Study Drug

After randomization, the treating investigator will order the treatment following this protocol dosing schema (see Tables 2 and 3). Commercial supply of ValA and ValG will be dispensed to the subjects.

6.6 Known Adverse Effects

As extracted from the package inserts for the study drugs, these are the known adverse effects for this protocol.

	Val G	**Val A**
COMMON Side Effects	headache	headache
	nausea	nausea
	abdominal pain	abdominal pain
	hematologic toxicity	
	diarrhea	
	fever	
	tremor	

	graft rejection vomiting hypertension upper respiratory infection urinary tract infection insomnia	
RARE adverse reactions	acute renal failure allergic reaction bleeding complications nervous system effects: agitation, hallucinations, confusion, delirium, seizures, swelling of the brain general pain, fatigue, weakness, edema abnormal lab results that might indicate abnormal organ function skin rash cough shortness of breath	acute renal failure allergic reaction bleeding complications nervous system effects: agitation, hallucinations, confusion, delirium, seizures, swelling of the brain

6.7 Subject Compliance Monitoring

Subjects will be asked to adhere to their prescribed treatment and dosage. Medication adherence will be assessed by the study team during routine visits, by reviewing the medical record, and by communication with the subject or guardian (table in section 5.4).

6.8 Prior and Concomitant Therapy

All prior and concomitant therapies will be documented and allowed as per standard of care procedures. Provided there are no direct interactions with the randomized medication, all medications will be prescribed as standard of care. Management of all viral disease is as per physician and will not be protocoled by research procedures.

6.9 Blinding of Study Drug

Not applicable.

7 Statistical Plan

7.1 Primary Study Endpoints

The primary study endpoints are as follows:

1. Incidence and duration of CMV and EBV viremia and magnitude of viremia as measured by area under the viral load-time curve of recipients who become viremic with CMV and/or EBV in the first year post-Ktx.
2. Incidence of subjects developing drug related side effects requiring dose reduction or cessation.
3. Presence of EBV and or CMV in renal tissue (protocol biopsies).

7.2 Secondary Study Endpoints

Organ donor and recipient demographics, transplant characteristics, donor/recipient infection history (pre-transplant EBV and CMV IgE antibody status and qPCR in donors and recipients.

7.3 Primary Safety Endpoints

Interim analysis will be done after the enrollment and completion of therapy with study drug valA or standard of care drug valG in 6 patients. If there is >= 20% increased incidence of CMV / EBV viremia in the valA cohort compared to the valG cohort then study will be stopped.

7.4 Statistical Methods

As per Lowance et al., 80% of the recipients that are randomized to the valA cohort will be CMV viremia free at 6 months. Therefore, to establish non-inferiority of valA as compared to valG, if I consider a difference less than 10% of no clinical importance, the required sample size with equal allocation between valA and valG to achieve an 80% power ($\beta=0.2$) at $\alpha=0.05$ we would need 54 recipients.

	CMV viremia free proportion	N in valA grp	N in valG grp	Total=119
CMV Ab+ R	80%	43	43	86
CMV Ab- R	84%	61	16	32

Since the anti-EBV effect of valG is unknown, a power calculation is impossible. Therefore we plan to include 200 recipients based on above sample size calculation and accounting for patient attrition etc.

8 Safety and Adverse Events

Definitions

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries will be regarded as adverse events.

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs a hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Known side effects of the study drug and of kidney transplant will not be treated as serious adverse events for this study unless they are life-threatening or fatal. See section 5.5 for a list of the known adverse effects of the study drugs. The known adverse effects of kidney transplant include:

- Graft dysfunction, including:
  - Delayed graft function
  - Failure of donor kidney
  - Rejection of the new kidney
  - Vascular thrombosis
- Recurrence of primary kidney diagnosis
- Severe infections
- Surgical complications
- Risks related to immunosuppression
- Risks related to steroids
- Hypertension
- Cardiovascular disease
- Diabetes
- Malignancy

Adverse Event Reporting Period
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition will be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality will be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event will also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events will be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator will instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if <u>any one of the following</u> conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization will be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.1 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results will be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.2 Reporting of Serious Adverse Events

8.2.1 Study Sponsor Notification by Investigator

A serious adverse event must be reported to the Principle Investigator within 24 hours of finding out of the event. Within the following 48 hours, further information on the serious adverse event must be documented in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form (see Appendix), and any other diagnostic information that will assist the understanding of the event. Significant new information of ongoing serious adverse events should be provided promptly to the PI. The PI will keep a copy of this SAE form on file at the study site. Report serious adverse events by phone and facsimile to:

Henry Balfour Jr, MD
612-625-3998
balfo001@umn.edu

At the time of the initial report, the following information should be provided:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

8.2.2 IRB Notification by Investigator

Reports of all serious adverse events (including follow-up information) must be submitted to the IRB within 5 working days if it falls under the expedited reporting

guidelines. Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's binder.

8.2.3 FDA Notification by Sponsor

The study sponsor shall notify the FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but no later than 7 calendar days from the sponsor's original receipt of the information.

If a previous adverse event that was not initially deemed reportable is later found to fit the criteria for reporting, the study sponsor will submit the adverse event in a written report to the FDA as soon as possible, but no later than 15 calendar days from the time the determination is made.

Agency	Criteria for Reporting	Timeframe	Form to Use	Submission address/fax numbers
U of MN IRB	Unanticipated death of a locally enrolled subject(s); New or increased risk; Any adverse event that requires a change to the protocol or consent form- refer to the IRB website for complete details	5 working days	UMN IRB Report Form	email to irb@umn.edu
	Other Problems or Events meeting the definition of Prompt Reporting per the IRB's website	5 working days	UMN IRB Report Form	email to irb@umn.edu
FDA	SAE: fatal, life-threatening, unexpected, at least possible related	7 calendar days	FDA MedWatch	– MedWatch Online Voluntary Reporting Form (www.accessdata.fda.gov/scripts/medwatch
	SAE: serious, unexpected, at least possibly related	15 calendar days		

8.3 Stopping Rules

This study may be terminated by the PI or DSMB at any time. Reasons for terminating the study may include the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects.
- Subject enrollment is unsatisfactory.
- Data recording is inaccurate or incomplete.

8.4 Medical Monitoring

The PI will oversee the safety of the study, including careful assessment and appropriate reporting of AEs. Medical monitoring will include a regular assessment of the number and type of SAEs.

8.4.1 Internal Data and Safety Monitoring Board

The study's Data and Safety Monitoring Plan will be compliance with the UMN Clinical and Translational Scientific Institute's Data & Safety Monitoring Plan (DSMB).

A DSMB will meet twice per year, with the first meeting occurring once approximately 25% of target enrollment has been accrued. The DSMB will review recruitment, participant status and subject safety associated with the trial and create a report for the Principal Investigator with their recommendations, if any, to the PI for the conduct of the study.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

Source data are contained in source documents Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

Data generated by the methods described in the protocol will be recorded in the subjects' medical records and/or study progress notes. Data may be transcribed legibly on CRFs supplied for each subject or directly inputted into an electronic system or any combination thereof.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

9.4 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 6 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 6 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

This study will be monitored according to FDA/GCP guidelines. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethical Considerations

To avoid participants forgetting their participation in the study, those subjects who begin active participation more than two months after their original consent will be contacted to confirm their interest in participation before they are randomized.

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of IRB members and their affiliate to the sponsor.

11.1 Informed Consent

All subjects' will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject using the IRB-approved consent form must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate and the Investigator-designated research professional obtaining the consent. A blank copy of the IRB-approved form must be kept on-site by the Investigator.

12 Study Finances

12.1 Funding Source

Study funding source is the Department of Surgery at the University of Minnesota.

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must refer to the Regents Policies on Individual Conflict of Interest Policy or Institutional Conflict of Interest Policy. These policies require University Faculty and staff to report external professional activities and business and significant financial interests related to his or her University activities by submitting a REPA (Report of External Professional Activities) at least once per year. Faculty and staff should also file a REPA when substantial changes in business or financial interests occur, when an activity that presents a potential conflict of interest is anticipated, or when submitting an application for research support or technology transfer, submitting research protocols to the IRB, or receiving financial contributions. All University of Minnesota investigators will follow the University conflict of interest policy.

13 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

14 References

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