Study Title:	A Phase II study of Xisomab 3G3, a monoclonal antibody preventing the activation of FXI by FXIIa, for the prophylaxis of catheter-associated thrombosis.
Protocol Number:	18976
Investigational product:	xisomab 3G3, AB023
Version Number:	3.0
Version Date:	5/25/2021
Replaces:	2.0
IND/IDE Status:	IND/IDE # **143558**
Principal Investigator:	**Joseph J. Shatzel, MD**
	Hematology and Oncology / Biomedical Engineering Oregon Health & Science University 3303 S BOND AVE PORTLAND OR 97239, CH13B Portland, OR 97239 Phone: 503-494-6594 Email: shatzel@ohsu.edu
Sub-Investigator(s):	Sven R. Olson MD Hematology and Oncology Oregon Health & Science University 3303 S BOND AVE PORTLAND OR 97239, CH13B Phone: 503-494-6594 Email: olsosv@ohsu.edu
Statistician:	Jeong Youn Lim, PhD Biostatistics Shared Resource, Knight Cancer Institute Oregon Health & Science University 3181 SW Sam Jackson Park Road, KR Phone: 503-494-7062 Fax: 503-346-6931 Email: limje@ohsu.edu
IRB Approved	1/27/2023
NCT#	NCT04465760

SUMMARY OF CHANGES

#	Section	Page(s)	Change	Justification
1.	see summary of changes memo			
2.	see summary of changes memo			
3.				
4.				
5.				

SYNOPSIS

Study Title	A Phase II study of Xisomab 3G3, a monoclonal antibody preventing the activation of FXI by FXIIa, for the prophylaxis of catheter-associated thrombosis.
Protocol #	18976
Study Center	OHSU, single-site
Clinical Phase	Phase 2 – single agent
Investigational Component	Investigational drug: xisomab 3G3
Interventional Study Type	*Single-arm*
Précis	Peripherally inserted central catheters (PICCs) and indwelling subclavian vein central venous catheters (ie, “Mediports”, “Port-a-Cath”, or “ports”) are frequently used in ambulatory cancer patients requiring chemotherapy, often remaining inserted for weeks to months. A major complication of central venous catheters is catheter-associated thrombosis (CAT), occurring in over 50% of patients. CAT can lead to substantial morbidity including pain, swelling, erythema, catheter occlusion, and the potential for thrombosis progression mandating anticoagulation. The anticoagulant treatment of CAT comes with inherent risks, including bleeding, increased healthcare costs surrounding the management and replacement of the catheter, and delays in cancer treatment. Previous studies have evaluated the role of traditional anticoagulants to prevent CAT but have failed to display favorable safety and efficacy profiles. Evaluation of contact activation factor (F) XII and FXI in device-associated thrombosis has demonstrated that inhibiting FXII or FXI reduces these thromboses in multiple animal models. FXII appears to be dispensable for hemostasis, as individuals with FXII deficiency have no bleeding diathesis, making it a promising target for antithrombotic therapy. Xisomab 3G3 is a first-in-class monoclonal antibody that binds to the A2 domain of FXI, preventing FXII-mediated FXI activation. Xisomab 3G3 has been shown to reduce device-associated thrombus formation in multiple preclinical models. In this phase 2 study, we will evaluate the safety and efficacy of a single dose of 2 mg/kg of xisomab 3G3 as prophylaxis against CAT in cancer patients having a catheter placed, as compared to historical controls. All participants in this trial will receive a single dose of xisomab 3G3 near the time of catheter placement. Study participants will undergo an upper extremity venous duplex ultrasound on day 14 (±4) after catheter placement to evaluate the occurrence of CAT (symptomatic or asymptomatic). All anti-cancer therapy provided to the participant while on-study will be at the discretion of the treating physician and in accordance with institutional guidelines. Safety follow-up will continue for 60 days from the date of catheter insertion, or until resolution or stabilization of any clinically significant drug-related adverse event, after which they will be considered off-study.
Primary Objectives	To evaluate the antithrombotic efficacy of prophylactic xisomab 3G3 treatment in cancer patients with a central venous catheter.

Secondary Objectives	To determine the safety and tolerability of prophylactic xisomab 3G3 treatment as measured by the incidence and severity of adverse events in cancer patients with a central venous catheter.
Exploratory Objective	Assessment of participant coagulation profiles, and the incidence of line occlusion requiring medical interventions to obtain patency.
Primary Endpoints	The number of participants with catheter-associated thrombosis, as defined by the total incidence of symptomatic and asymptomatic thrombosis, and thrombotic occlusion leading to device failure (start: administration of xisomab; end: Day 18)
Secondary Endpoints	The number of subjects with treatment-related adverse events (TRAEs) and treatment-emergent adverse events (TEAEs) will be summarized using frequency counts (start: time of consent, end: Day 60)
Exploratory Endpoints	Quantification of coagulation parameters and assessment of catheter occlusion (start: pre-dose, end: Day 18 [i.e., post-dose]): a. Activated partial thromboplastin time (aPTT) b. Pharmacokinetic (PK) evaluation c. Time to symptomatic catheter-associated thrombosis d. Proportion of participants with a catheter occlusion requiring medical intervention
Number of Participants	A total of 50 participants will be enrolled.
Duration of Therapy	1 day
Duration of Follow Up	60 days [post catheter placement]
Key Inclusion Criteria	• Men and women, aged ≥ 18 years and members of all races and ethnic groups will be included. • Participants with any solid tumor malignancy that will undergo insertion of a central venous catheter (PICC or indwelling subclavian vein central venous catheter) as part of planned cancer-directed therapy per institutional standards • Able to wait 1 day post-study drug infusion before receiving cancer-directed therapy. • ECOG performance status ≤2 • Expected life expectancy of >6 months • At time of enrollment, must have adequate platelet count (>100 x 10^9/L)
Key Exclusion Criteria	• Concurrent participation in another therapeutic clinical trial • Leukemia (lymphoma and myeloma may be included) • ≤72 hours since major surgery • Abnormal renal function defined by an eGFR < 45 mL/min • Abnormal hepatic function defined as LFTs (AST, ALT or Total Bilirubin) >2x the upper limit of normal or known Child-Pugh class B or C cirrhosis. • Abnormal baseline coagulation profile: o INR > 1.5 or aPTT prolonged. • Prior history of intracranial hemorrhage • Primary brain tumors or known brain metastasis

	• Major extracranial bleed within the last 6 months where the cause has not been identified or treated • Use of oral anticoagulation at enrollment • Known bleeding diathesis • At the discretion of the investigator, any other contraindication to anticoagulation therapy • Previously documented hypersensitivity to either the drug or excipients • Participant is pregnant or breastfeeding • Participant is expected to receive chemotherapy associated with a 15% or higher incidence of grade 3-4 thrombocytopenia • Allergy to heparin and heparin derivatives • History of venous thromboembolism (VTE) within the last 3 months.
Investigational Product	Xisomab 3G3 (2 mg/kg) is a recombinant, humanized, monoclonal IgG4 antibody that functions as a contact activation inhibitor and an anticoagulant by binding FXI and preventing FXI activation by FXIIa.
Statistical Considerations	The basis for our sample size calculation is the assumption of a 60% incidence of ultrasound-confirmed CAT (symptomatic or screened) over 18 days post-catheter placement in historical controls, informed by prior studies of cancer patients with venous catheters. A sample size of 50 patients, accounting for a 4% efficacy analysis ineligibility rate, was calculated to provide 80% power to detect a 20 percentage point decreased incidence of CAT at a two-sided alpha level of 0.05.

SCHEMATIC OF STUDY DESIGN

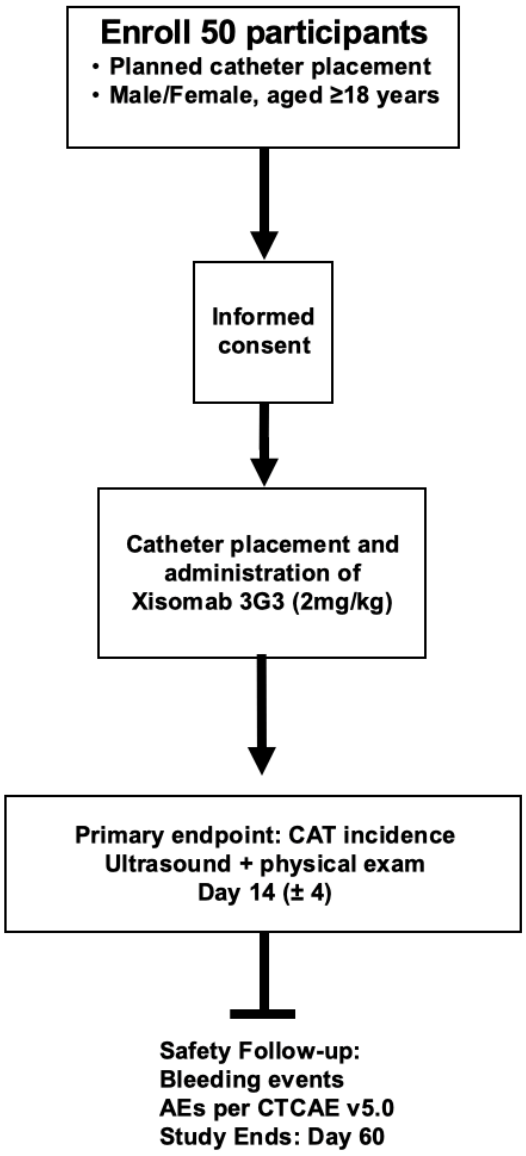

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the curve
BUN	Blood urea nitrogen
CAT	Catheter-associated thrombosis
CBC	Complete blood cell (count)
CFR	United States Code of Federal Regulations
CoC	National Institutes of Health (NIH) Certificate of Confidentiality
CRC	Clinical Research Coordinator
CRMS	Clinical research management system
CRQA	Clinical Research Quality & Administration
CRRC	Clinical Research Review Committee (OHSU)
CRF	Case report form
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTMS	Clinical Trial Management System
DLT	Dose limiting toxicity
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
eCRIS	Electronic Clinical Research Information System
EDC	Electronic data capture
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
HCT	Hematocrit
HGB	Hemoglobin
HIPPA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational new drug application
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
IV	Intravenous
LFT	Liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
OHRP	Office for Human Research Protections
OHSU	Oregon Health & Science University
PET	Positron emission tomography
PI	Principle Investigator

PICC	Peripherally inserted central catheter
PK	Pharmacokinetics
PO	*Per os* (by mouth, orally)
(a)PTT	(activated) Partial thromboplastin time
RBC	Red blood cell (count)
RP2D	Recommended Phase II Dose
RNI	Reportable new information
SAE	Serious adverse event
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
tPA	tissue plasminogen activator
TSMP	Trial Specific Monitoring Plan
UA	Urinalysis
ULN	Upper limit of normal
UP	Unanticipated problem
WBC	White blood cell (count)

1. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 OVERVIEW OF CATHETER-ASSOCIATED THROMBOSIS

Peripherally inserted central catheters (PICCs) and indwelling central catheters are commonly used in both hospitalized and ambulatory patients who require centrally acting, or chronic intravenous (IV) medications including vasoactive drugs, antibiotics and chemotherapy. PICC lines are inserted through the peripheral veins of the upper extremity with the end of the catheter positioned above the patient's right atrium (**Figure 1**). PICCs offer many conveniences including limiting the need for further venipuncture and easy bedside insertion and removal; however, they are associated with high rates of complications including occlusion and/or mis-positioning, infection, and most commonly thrombosis.[1] Catheter use is exceedingly common in modern health care (Centers for Disease Control [CDC] data suggest approximately 30% of hospitalized medical patients have a central venous catheter placed), and at least 5 million central venous catheters are inserted in the US annually. As such, measures to decrease common complications would have a large patient impact.[2,3]

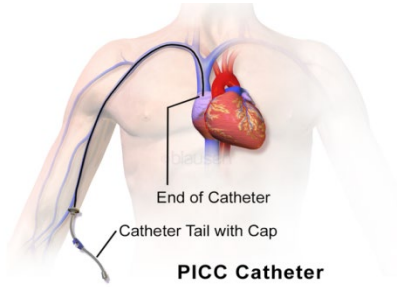

Figure 1. Anatomic placement of peripherally inserted central venous catheter.

Source: Blausen Medical Communications.

Thrombosis complicates over half of PICC lines. Rates of screened thrombosis vary due to heterogeneity in patient population, catheter type, and anticoagulation use, but incidences between 50-60% are generally reported at 14 days post insertion, with one study reporting a 61% incidence at 12-14 days in patients not on anticoagulation, and another 72% at 14-28 days.[4,5] While many of these thromboses remain occult, about 5-7% of patients will develop symptomatic thrombosis leading to patient morbidity, increased healthcare utilization and delays in medical care.[6] Likewise, indwelling central venous catheters (ie, "Mediports", "Port-a-Cath", or "ports") are plagued by high rates of thrombosis. Rates of CAT up to 62% have been reported in cancer patients not on anticoagulation.[7]

Cancer patients commonly have central catheters placed to allow for chemotherapy and routine laboratory evaluation. Cancer is also a prothrombotic state, leading to a significantly higher risk for venous thromboembolism than the general population. Prospective studies specific to cancer patients with PICCs receiving weekly screening ultrasounds note a 51.4 % CAT rate, with a mean dwell time from PICC insertion to thrombosis of 8-11 days. (**Figure 2**).[8,9] Multiple prior studies have evaluated chemoprophylaxis in cancer patients with central catheters to prevent CAT, however traditional anticoagulants have failed to display a favorable safety to efficacy ratio.

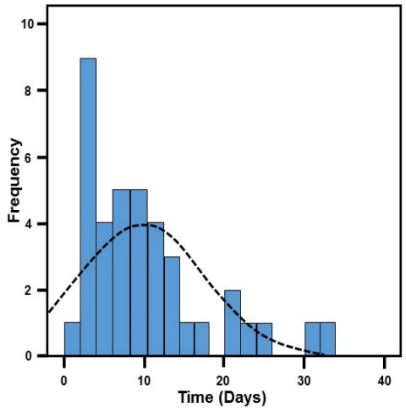

Figure 2. Average dwell time until CAT detection.

CAT and its treatment incur significant morbidity and costs. Current guidelines from three different professional societies all recommend initiation of anticoagulation upon the detection of CAT, and continuing anticoagulation for 3-6 months following catheter removal.[10-12] However, this strategy incurs a notable bleeding risk. A systematic review of multiple studies of patients with CAT treated with anticoagulation found rates of major hemorrhage up to 4.9%, with some series reporting bleeding rates approaching

25%.[13,14] Besides patient morbidity, CAT incurs significant expense. The estimated costs of iatrogenic/preventable venous thrombosis in the United States is over $7.5 billion USD annually.[15] Estimates of the direct medical costs of treating a patient with venous thrombosis range from of $12,000 to $15,000 (2014 US dollars).[16]

Given the significant burden and costs associated with CAT multiple prospective trials[17] and meta-analysis[18] have evaluated the role of prophylactic anticoagulation to prevent CAT. The current literature has failed to show convincing evidence to support routine prophylaxis in all-comers with central venous catheters, but have shown a concerning risk of bleeding with traditional anticoagulants. In certain high-risk prothrombotic subsets such as cancer patients, anticoagulation may be effective at decreasing symptomatic CAT. One large meta-analysis found the absolute incidence of symptomatic CAT was reduced from 6.8% to 3.7% (P<0.001) in cancer patients given prophylactic anticoagulation, with 32 patients (95% CI, 21 to 65) needed to be treated to prevent one symptomatic event.[6] Guidelines from four major cancer professional societies recommend against routine prophylactic anticoagulation, however, citing insufficient evidence of benefit and prohibitive bleeding risks.[19]

Given the significant morbidity and financial burden associated with CAT, and the inability of traditional anticoagulants to safely prevent CAT, development of prophylactic interventions that are effective, but do not increase bleeding risk remains an unmet medical need.

1.2 **OVERVIEW OF XISOMAB 3G3**

Xisomab 3G3 is a novel anticoagulant recombinant monoclonal antibody directed against coagulation factor XI (FXI). Please refer to investigator brochure for detailed information.

1.2.1 MECHANISM OF ACTION

The intrinsic pathway of thrombin generation starts with assembly and activation of the contact complex comprising FXII, high molecular weight kininogen (HK), prekallikerin (PK), and FXI.[20,21] Activated FXI (FXIa) further activates FIX, which in turn acts with its cofactor (FVIII) to form the tenase complex on a phospholipid surface to activate FX, ultimately leading to thrombin generation. Whereas deficiencies of FVIII and FIX lead to haemophilia A and B, respectively, individuals lacking FXII, PK, or HK do not bleed abnormally.[20] Xisomab 3G3 is a humanized IgG4 mouse monoclonal antibody designed to bind to the FXI A2 domain, thus interfering with the assembly of the contact activation complex and reducing PK, FXI and FXII interactions and activation. As such, xisomab 3G3 acts as a functional inhibitor of pathological FXIIa by preventing prothrombotic contact activation of FXI by FXIIa and FXIa without substantially interfering with vasoregulatory activities of FXIIa, enzymatic activity of FXIa, or hemostatic FXI feedback activation by thrombin.

1.2.2 PRE-CLINICAL EXPERIENCE

Xisomab 3G3 has been evaluated to examine its binding profile to human tissues as well as its ability to induce cytokine release and antibody-dependent cell mediated cytotoxicity. The safety and toxicokinetics of xisomab 3G3 have been evaluated in pivotal single dose studies in both rats and cynomolgus monkeys (refer to investigator brochure for details). In cynomolgus monkeys, intravenous administration of xisomab 3G3 (10 mg/kg dose) was associated with a group mean terminal elimination half-life ($T_{½}$) of 31.9 hours (range: 65.9 hours at 2 mg/kg to 212 h at 50 mg/kg). No adverse effects were observed up to a maximal dose tested of 50 mg/kg. Preclinical data also demonstrate a prolongation of aPTT in all species tested, including in vitro studies using human plasma that is expected due to its mechanism of action.

1.2.3 CLINICAL STUDIES OF XISOMAB 3G3

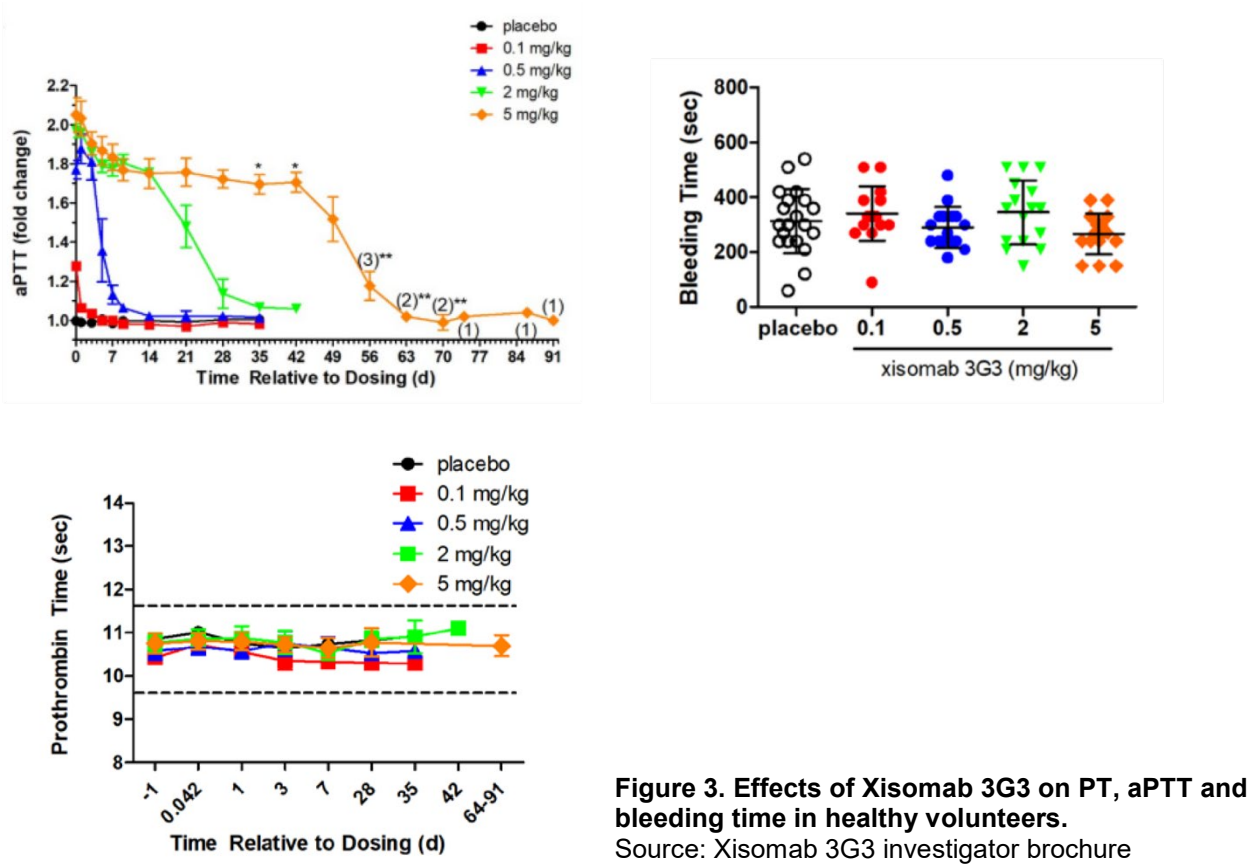

Figure 3. Effects of Xisomab 3G3 on PT, aPTT and bleeding time in healthy volunteers.
Source: Xisomab 3G3 investigator brochure

The safety of xisomab 3G3 was initially assessed in a phase 1 trial of 21 healthy adults (clinicaltrials.gov). The trial evaluated single dose of xisomab 3G3 at concentrations of 0.1, 0.5, 2.0 or 5 mg/kg, or placebo. The primary endpoint was treatment related adverse events. The most common treatment emergent adverse event (TEAE) was productive cough, considered unrelated or unlikely treatment related and experienced by 2 (13%) subjects. All other AEs were experienced by 1 subject. Xisomab 3G3 prolonged activated partial thromboplastin time (aPTT) in a dose dependent manner, suggesting effective inhibition of FXI activation by FXIIa, while having no appreciable effect on bleeding and prothrombin times (**Figure 3**).

1.3 **RATIONALE**

Contact activation-induced thrombin generation can be initiated by artificial, negatively charged surfaces, and has been implicated as a major driver in the development of device associated thrombosis. FXI and FXII may be instrumental in the development of catheter associated thrombosis and they could be good therapeutic targets for safe prophylaxis. Catheters coated with a potent inhibitor of FXII activation, corn trypsin inhibitor, significantly delayed the development of CAT in vitro and in vivo[22], as did knockdown of FXII in mice.[23] Antibodies targeting FXIIa also prevented thrombosis in a rabbit model of extracorporeal circulation and reduced accumulation of clots in blood-perfused membrane oxygenators in baboons.[24] FXII appears to be completely dispensable for hemostasis, as individuals born FXII deficient have no

bleeding diathesis or other known pathology.[25] While individuals born deficient in FXI (hemophilia C) can have a mild bleeding diathesis, a human trial using antisense invoked FXI deficiency for surgical thromboprophylaxis found that humans significantly deficient in FXI can safely undergo orthopedic surgery without any significant increases in bleeding, when compared to enoxaparin, and are protected against thrombosis.[26] Thus, inhibition of the contact activation complex (FXII, FXI, PK and HK), holds promise as a prophylactic intervention to prevent device associated thrombosis without increasing bleeding risk.

This study seeks to assess the safety and efficacy of xisomab 3G3 in reducing the occurrence of CAT in cancer patients undergoing placement of a central venous catheter. The antibody will be administered as a single dose of 2mg/kg within 48 hours (±2 days) of catheter insertion. This dose is based on pharmacokinetic data obtained in the phase 1 trial showing consistent evidence of pharmacodynamic effect (elevated aPTT) at day 14 which was normalized by day 28 (**Figure 3**).

1.4 **POTENTIAL RISKS AND BENEFITS**

1.4.1 KNOWN POTENTIAL RISKS

The safety profile of xisomab 3G3 in humans is still being established. Xisomab 3G3 functions to inhibit, among others, contact activation of the intrinsic blood coagulation cascade. While inhibition or lack of FXII, PK, and HK do not appear to impair hemostasis, it is not yet known if interference with contact-mediated auto-activation of FXI has clinically relevant antihemostatic consequences. This may interfere with hemostatic function, thus increasing the risk for bleeding. Results of the completed phase 1 study (n = 21), following administration of xisomab 3G3, showed no severe, dose-dependent hemostasis-related adverse effects. As a humanized antibody, participants receiving xisomab 3G3 may develop a variety of acute or delayed allergic reactions, such as rash, edema, urticaria, asthma, blood pressure changes, as well as severe anaphylaxis. No severe allergic reactions to xisomab 3G3 were observed in the phase 1 trial. Refer to investigator brochure for further details.

1.4.2 KNOWN POTENTIAL BENEFITS

Inhibiting contact activation with xisomab 3G3 may reduce the incidence of CAT in patients that have a central venous catheter as part of their planned anti-cancer therapy. This may reduce CAT-associated morbidity and unwanted delays in cancer treatment. It cannot, however, be guaranteed that participants in this study will directly benefit from treatment during participation, as the clinical trial is designed to provide information about the safety and effectiveness of the investigational approach.

2. STUDY DESIGN AND ENDPOINTS

2.1 DESCRIPTION OF THE STUDY DESIGN

Refer to Section 8*, Statistical Considerations, for additional information regarding statistical methods used in this study.*

This is a phase 2, single center, single arm trial to assess the safety and efficacy of xisomab 3G3 in reducing the incidence of CAT in cancer patients undergoing PICC insertion or indwelling catheter placement. Participants must meet the inclusion criteria, have none of the exclusion criteria, and have provided written informed consent before the conduct of any screening tests not performed routinely in their treatment.

A total of 50 participants are planned for enrollment into this study. Eligibility will be confirmed prior to planned PICC line placement or indwelling central venous catheter placement. Eligible participants that are scheduled to have a catheter inserted as part of their planned anticancer therapy will be enrolled to receive xisomab 3G3. Within 48 hours of insertion of the PICC or indwelling catheter (i.e. ± 2 days) per institutional standards, participants will undergo IV placement and receive a single dose of xisomab 3G3. Standard procedures for catheter maintenance for sterility and patency will be performed each time the catheter is accessed for use including 10 to 20 ml of normal saline pulsatile flush before and after use and every 7 days in the outpatient setting. Two days after administration of xisomab 3G3 participants may proceed with planned, standard-of-care anticancer treatment in consultation with their treating physician and in accordance with institutional guidelines. The **primary objective** is to measure the efficacy of xisomab 3G3, as determined by the incidence of ultrasound-confirmed CAT (both symptomatic and asymptomatic) within 18 days after catheter insertion, compared to historical cancer controls. All participants will undergo duplex venous ultrasound and physical examination to evaluate symptomatic or asymptomatic CAT at 14 (± 4) days after catheter placement. If participants develop symptoms suggestive of CAT such as arm pain, swelling, or erythema in the arm with the PICC, those participants will undergo standard-of-care workup with a unilateral extremity duplex venous ultrasound in the affected arm or leg. Participants that have confirmed CAT or other thrombosis found on imaging, per investigator assessment, will be treated at the discretion of their treating physician per institutional guidelines and standards of care. The duplex venous ultrasound assessment will include evaluation of disease history and physical exam to further assess possible thrombosis-associated symptoms. The **secondary objective** is to establish the safety and tolerability of xisomab 3G3 administered near the time of central line placement in patients that are diagnosed with and treated for solid tumors. All participants will be followed for 60 days (or until resolution/stabilization of any clinically significant drug-related adverse event) from time of catheter insertion to assess for AEs and medication use.

2.2 STUDY OBJECTIVES AND ENDPOINTS

2.2.1 PRIMARY OBJECTIVE AND ENDPOINT

Objective	Endpoint	Start	End
To determine the efficacy of xisomab as measured by the incidence of CAT in individuals with a central venous catheter	Incidence of CAT	Catheter insertion (Day 1)	Day 18

2.2.2 SECONDARY OBJECTIVES AND ENDPOINTS

Objective	**Endpoint**	**Start**	**End**
To evaluate the safety and tolerability of xisomab 3G3 in cancer patients with a PICC or indwelling catheter	1. Incidence of major and clinically-relevant bleeding [refer to Section 6.1.9.1] 2. Incidence of xisomab 3G3-associated toxicities [per CTCAE v5.0]	Administration of xisomab 3G3 (Day 1 ± 2 days)	End of follow-up (Day 60)

2.2.3 EXPLORATORY OBJECTIVE AND ENDPOINT

Objective	**Endpoint**	**Start**	**End**
Assessment of drug exposure and catheter occlusions leading to medical intervention	Quantification of coagulation profile: 1. aPTT 2. PK evaluation 3. Time to thrombosis (i.e., symptomatic CAT) 4. Proportion of participants with a catheter occlusion requiring medical intervention (i.e., local administration of tPA)	pre-xisomab 3G3 administration	Day 18

3. STUDY ENROLLMENT AND WITHDRAWAL

3.1 PARTICIPANT INCLUSION CRITERIA

To be eligible to participate in this study, an individual must meet all of the following criteria:

1. Participant or legally authorized representative (LAR) must provide written informed consent before any study-specific procedures or interventions are performed.
2. Men and women, aged ≥ 18 years.
3. In consultation with PI and treating physician, participant's cancer-directed therapy allows for a 1-day period between administration of study drug and subsequent start of planned cancer-directed therapy.
4. Individuals with a confirmed solid malignancy that will undergo insertion of a PICC line or indwelling central venous catheter as part of planned anticancer therapy per institutional standards
5. Must have ECOG performance status ≤ 2 (refer to Appendix A)
6. At time of enrollment, must have:
   a. Platelet count > 100 x 10^9/L,
7. Female participants of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

   Participants of childbearing potential are defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal.
8. Female participants of childbearing potential must agree to use adequate methods of contraception (Appendix B) starting with the first dose of study therapy through 90 days after the last dose of study therapy.

   Participants of childbearing potential are those who have not been surgically sterilized or have not been free from menses for >1 year without an alternative medical cause.
9. Male participants must agree to use an adequate method of contraception (Appendix B) starting with the first dose of study therapy through 90 days after the last dose of study therapy.

3.2 PARTICIPANT EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Actively receiving treatment in another therapeutic clinical trial
2. Active acute leukemia (lymphoma and myeloma are allowed)
3. At time of enrollment, known contraindication to anticoagulation therapy, including:
   a. Clinically significant active bleeding

b. Individual is within 72 hours of major surgery
c. Abnormal baseline coagulation tests, including INR > 1.5, or aPTT prolonged
d. Abnormal renal function defined by an eGFR < 45 mL/min
e. Abnormal hepatic function defined as LFTs (AST, ALT or Total Bilirubin) >2x the upper limit of normal or known Child-Pugh class B or C cirrhosis.
f. Prior history of intracranial hemorrhage
g. Primary brain tumors or known brain metastasis
h. Major extracranial bleed within the last 6 months where the cause has not been identified or treated
i. Known bleeding diathesis
j. Use of therapeutic anticoagulation or anti-platelet agents for any indication at enrollment
k. At the discretion of the investigator, any other contraindication to anticoagulation therapy
l. Presence of a pediatric-sized PICC line
m. Participant is expected to receive chemotherapy associated with a 15% or higher incidence of grade 3-4 thrombocytopenia within 14 days of recieving study drug.

4. Preexisting intravenous catheter, or indwelling spinal or epidural catheter, at time of enrollment that is intended to remain for the duration of study. Participants may remain eligible if existing catheter is to be removed before placement of a catheter for cancer directed therapy. Removal of existing catheter should occur at least 24 hours prior to PICC or indwelling catheter insertion.
5. Previously documented hypersensitivity to either the drug or excipients
6. Psychiatric illness/social situations, or any other condition, that in the opinion of the investigator, would limit compliance with study requirements
7. Participant is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 90 days after the last dose of trial treatment.
8. Participant is allergic to heparin or heparin derivatives.
9. Participants with a history of venous thromboembolism within the last 3 months.

3.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Participants for this study will primarily be recruited from hematology and oncology practices within OHSU, including affiliated community hematology and oncology (CHO) practices. Participants may be identified and referred to this study by their primary treating physician from within OHSU/CHO, or from the outside community. Participants may be identified by a member of the patient's treatment team, the PI, research team, or medical and surgical oncology clinics part of OHSU/CHO. As a member of the treatment team, the investigator will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Referral of potential participants to investigator of this study is made as part of standard of care, with the referring physician seeking advice on the diagnosis, evaluation, and/or treatment of the patient's malignancy.

The investigators may also screen the medical records of potential participants with whom the investigator does not have a treatment relationship. This will be done for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these potential individuals regarding the possibility of participating in the study. Participants may also initiate contact with the investigator through information of this study posted on the clinicaltrials.gov website.

3.3.1 ACCRUAL ESTIMATES

No OHSU Knight Cancer Institute study will focus on any particular gender, racial or ethnic subset. No participant will be excluded from the study on the basis of sex, gender, racial or ethnic origin. Male, female and minority volunteers will be recruited for this study from the general population and approximately 50% men and 50% women will be studied. Gender-nonconforming and gender-fluid individuals as members of the general population will also be recruited. The projected sex, gender, racial, and ethnic composition of the study will represent that of the state of Oregon (**Table 1**).

Table 1. Oregon Population Demographics and Projected Accrual

Ethnic Category [OR]	**Sex/Gender**					
	Females		**Males**		**Total**	
	n	*%*	n	*%*	n	*%*
Hispanic or Latino	3	*6.5*	3	*6.3*	6	*12.8*
Not Hispanic or Latino	22	*44.0*	22	*43.2*	44	*87.2*
Ethnic Category: Total of all participants*	25		25		50	*100**
Racial Category						
American Indian or Alaskan Native	0	*0.9*	0	*0.9*	1	*1.8*
Asian	1	*2.3*	1	*2.2*	2	*4.5*
Black or African American	1	*1.1*	1	*1.0*	1	*2.1*
Native Hawaiian or other Pacific Islander	0	*0.2*	0	*0.2*	0	*0.4*
White	22	*44.1*	22	*43.3*	44	*87.4*
Two or more races	1	*1.9*	1	*1.9*	2	*3.8*
Racial Category: Total of all participants*	25	*50.5*	25	*49.5*	50	*100*

Source: Adapted from U.S. Census Bureau, 2017.
*Totals may not equal 100 due to rounding.

3.3.2 INCLUSION OF CHILDREN

This study will not include children or adolescents as the safety profile of xisomab 3G3 has not been evaluated in a pediatric population.

3.4 **REGISTRATION PROCEDURES**

3.4.1.1 *OHSU Registration*

Participants will be required to give written informed consent to participate in the study before

any screening tests or evaluations are conducted that are not part of standard care.

Registration from all consented participants must be entered into the OHSU electronic Clinical Research Management System (CRMS, e.g., eCRIS). At a minimum, registration of OHSU participants will include signed copies of the most recently IRB-approved, informed consent form and HIPAA authorization.

3.5 PARTICIPANT SCREENING AND ENROLLMENT

In order to participate in this study, signed informed consent must be obtained from the participant or the participant's legally acceptable representative. The current Institutional Review Board (IRB) approved informed consent must be signed and dated by each participant prior to undergoing any study procedures or before any prohibited medications are withheld from the participant in order to participate in this study.

Screening will begin once the participant has provided written informed consent to participate in the study . All screening and baseline evaluations will be performed during the screening phase (i.e., up to 28 days before catheter placement). Day 1 of the clinical trial will be when the central venous catheter is inserted. Total accrual of all participants is anticipated to take a total of 36 months.

3.6 PARTICIPANT WITHDRAWAL OR DISCONTINUATION

Participants are free to withdraw consent and discontinue participation in the study at any time and without prejudice to further treatment.

If a participant withdraws consent, they will be specifically asked if they are withdrawing consent to:

- All further participation in the study including any further follow up
- Withdrawal of consent to the use of their study generated data
- Withdrawal to the use of any biological samples

No further participant contact should be made if the participant withdraws consent for participation in the study. Information about the reason(s) for discontinuation and collection of any new or ongoing AEs and medications should be collected at the time the participant withdraws consent.

For all other reasons for discontinuation from the study treatment phase, the participant should return to the clinic for the end of treatment (EOT) visit according to Section 6, Study Procedures/Evaluations And Schedule

3.6.1 HANDLING PARTICIPANT WITHDRAWAL AND DISCONTINUATION

Participants enrolled in this study that withdraw prior to receiving study drug will be replaced.

3.7 OFF-STUDY CRITERIA

Criteria that can take a participant off-study include:

- Participant requests to be withdrawn from study without further follow-up,
- Participant is lost to follow-up,
- Participant completes study follow-up period,

- Death,
- Screen failure,
- Investigator's discretion

3.7.1 SCREEN FAILURES

Any participant that has signed the consent form but does not meet the study eligibility criteria, or meets study eligibility criteria but terminates their participation prior to receiving study treatment, will be considered a screen failure. The reason for screen failure should be captured in the database for each participant failing to meet the eligibility criteria.

3.8 **STUDY DISCONTINUATION**

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to IRB and manufacturer. If the study is prematurely terminated or suspended, the Investigator will promptly inform the IRB and the manufacturer and will provide the reason(s) for the termination or suspension.

Reasons for terminating the study may include the following:

- Incidence or severity of adverse events, in this or other studies, indicates a potential health hazard to participants.
- Data that are not sufficiently complete and/or evaluable.
- Investigators do not adhere to the study protocol, or applicable regulatory guidelines in conducting the study.
- Participant enrollment is unsatisfactory.
- Submission of knowingly false information from the study site to manufacturer or regulatory authorities.
- Upon instruction by local or other regulatory, or oversight authority.

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the Sponsor/manufacturer, IRB and/or FDA.

4. INVESTIGATIONAL PRODUCT

A list of the adverse events and potential risks associated with the investigational or other agents administered in this study can be found in Section 7.4, Adverse Events.

4.1 **XISOMAB 3G3**

Xisomab 3G3 is a humanized IgG4 monoclonal antibody manufactured by Aronora, Inc. Refer to investigator brochure for additional details.

4.1.1 ACQUISITION

Xisomab 3G3 will be supplied by the manufacturer, Aronora Inc., and prepared by the research pharmacy services at OHSU per manufacturer instructions. Following submission and approval of the required regulatory documents, a supply of xisomab 3G3 may be ordered from Aronora Inc. by completing a Drug Request Form.

4.1.2 FORMULATION, APPEARANCE, PACKAGING AND LABELING

The 146 kDa antibody, xisomab 3G3, is produced as a lyophilized cake that is formulated in 8% sucrose, 10 mM histidine, 30 mM arginine HCl, 10 mM methionine, 80 ppm polysorbate 80, and has a pH of ~5.2 after reconstitution for intravenous administration. Xisomab 3G3 is packaged in a 10 mL nominal-volume USP-Type I colorless glass vial, stoppered with a bromobutyl rubber stopper and capped with an aluminum overseal with a flip-off cap. Vials containing xisomab 3G3 will denote drug product as being intended for investigation only. The lyophilized cake white is slightly yellow, clear and colorless liquid upon reconstitution.

4.1.3 PRODUCT STORAGE AND STABILITY

The lyophilized xisomab 3G3 drug product should be stored upright at 2°C to 8°C. The drug product is stable for 36 months if stored at these conditions. Exposure to bright light should be avoided; standard room illumination does not necessitate any precautions. Once reconstituted, xisomab 3G3 is stable for at least 6 hours when stored at 25°C.

4.1.4 COMPATIBILITY

Lyophilized xisomab 3G3 should be reconstituted in sterile water for injection.

4.1.5 HANDLING

Aseptic technique, use of sterile disposable gloves and hand hygiene according to institutional standards. Manufacturer recommends disinfection of the septum of the injection stoppers using a swab with an appropriate disinfectant (based on ethanol or isopropanol).

4.1.6 PREPARATION

Per manufacturer instructions, lyophilized xisomab 3G3 should be reconstituted with 2.6 ml sterile water for injection by carefully dispensing diluent into the vial of lyophilizate, trying to maintain the product and liquid in the base of the vial to avoid having the powder distribute around the walls of the vial. Gently swirl the vial content until the lyophilized drug product is completely dissolved and the solution is homogenous and transparent (not cloudy) when held against light. The final volume should result in 2.8 mL of reconstituted xisomab 3G3 antibody

drug product for administration. The final nominal concentration of xisomab 3G3 following reconstitution is 15 mg/mL. Multiple doses may be administered from one drug product vial.

4.1.7 ADMINISTRATION

The reconstituted drug product should be administered intravenously via a peripherally inserted IV line or via the catheter as a slow bolus (approximately 1 minute) within 48 hours of catheter placement (i.e. +/- 2 days).

4.1.8 SPECIAL CONSIDERATIONS FOR ADMINISTRATION

Xisomab 3G3 is to be administered at a fixed dose of 2 mg/kg. The participant's weight should be measured prior to administration. To calculate the exact volume of concentrated solution needed for the dose, apply the following equation:

$$V_{dose}(mL) = \frac{[Dose\ (mg/kg)\ x\ Body\ weight\ (kg)]}{15\ (mg/mL)}$$

Example: for a 70 kg patient dosed at 2 mg/kg, then:

$$V_{dose}(mL) = \frac{\left[2\ \left(\frac{mg}{kg}\right) x\ 70\ (kg)\right]}{15\ \left(\frac{mg}{mL}\right)} = 9.3\ ml\ xisomab\ 3G3$$

To calculate the number of vials needed for the dose follow these steps:

$$Participant\ dose\ (vials) = \frac{V_{dose}(mL)}{2.8\ mL}$$

If result is obtained with decimals, it should be rounded up to the nearest upper unit

Example: for a 70 kg patient dosed at 2 mg/kg, the calculated patient dose is 3.3 vials, then 4 vials should be used to obtain the volume of concentrated solution.

4.1.9 ACCOUNTABILITY

RPS will maintain a careful record of the inventory and disposition of the study agent. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage).

Responsibility for drug accountability at the study site rests with the Investigator; however, the Investigator may assign some of the drug accountability duties to an appropriate pharmacist or designee. Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities or other oversight bodies.

The Investigator or designee will collect and retain all used, unused, and partially used containers of study medication until full accounting has been completed. The Investigator or designee must maintain records that document:

- Investigational product delivery to the study site.
- The inventory at the site.

- Use by each participant including unit counts from each supply dispensed.
- Return of investigational product to the Investigator or designee.
- Destruction or return of investigational product for final disposal.

These records should include dates, quantities, batch/serial numbers (if available), and the unique code numbers (if available) assigned to the investigational product and study participants.

The investigational product must be used only in accordance with the protocol. The Investigator will also maintain records adequately documenting that the participants were provided the correct study medication specified.

Completed accountability records will be archived by the site. At the completion of the study, the Investigator or designee will oversee shipment of any remaining study drug back to Aronora Inc. for destruction according to institutional standard operating procedures. If local procedures mandate site destruction of investigational supply, prior written approval must be obtained from Aronora Inc.

4.1.10 DESTRUCTION AND RETURN

At the end of the study unused supplies of study drug should be destroyed according to institutional policies. Drug supplies will be counted and reconciled in full at the site with all monitoring procedures complete before destruction. Destruction will be documented in the Drug Accountability Record Form.

5. TREATMENT PLAN

5.1 DOSAGE AND ADMINISTRATION

Treatment will be administered on an *out-patient* basis. Reported adverse events and potential risks are described in Section 7.4, Adverse Event List.

Regimen Description			
Agent	*Dose*	*Route***	*Schedule*
Xisomab 3G3	2 mg/kg	IV (via catheter)	Single dose administered within 48 hours of catheter placement (± 2 days).
. ***Study drug should be administered as a slow bolus (approximately 1 minute).*			

Enrolled participants will receive a single fixed dose of xisomab 3G3 (2 mg/kg) through a peripheral IV or the inserted catheter within 48 hours of catheter placement (i.e. ± 2 days). If Xisomab 3G3 is administered prior to D1 catheter placement, eligibility must be confirmed prior to study drug administration. Participants will be monitored for at least 1 hour on the day of xisomab 3G3 administration for adverse events. Participants not receiving study drug or catheter placement as scheduled, may be rescheduled if within allowable screening window (i.e., no more than 28 days from consent). Participants receiving study drug but have a delay in placement of the catheter beyond 48 hours from time of xisomab administration, will not be considered evaluable for efficacy analysis (per Section 8.1), but will be followed for xisomab 3G3-associated toxicities (per Section 6.7).

Two (2) days after participants receive study drug they may proceed to undergo planned anticancer therapy per standard of care. Administration of planned cancer-directed therapy may not occur earlier than 2 days from time of giving study drug. The type(s) and frequency of administration of anticancer drug(s) comprising the participants' anticancer treatment regimen is at the discretion of treating physician and should be recorded in the CRF.

Consistent with institutional standards, participants may at any time during the study receive a standard of care workup with an ultrasound if they develop symptoms the investigator (or treating physician) believes to be suggestive of CAT, including arm pain and swelling or erythema in the same arm as the catheter. In such cases, the participant may receive antithrombotic therapy, at the discretion of their treating physician, per institutional guidelines.

5.2 TREATMENT PERIOD

After administration of a single, fixed dose of xisomab 3G3 (2 mg/kg) within 48 hours of catheter placement (with this placement defining Day 1), participants will undergo an end of treatment visit on Day 14 (± 4 days).

5.3 CONCOMITANT MEDICATION AND SUPPORTIVE CARE GUIDELINES

Medications required to treat AEs, treat cancer, manage cancer symptoms, concurrent diseases and supportive care agents, such as pain medications, anti-emetics and anti-diarrheals are allowed in general. The participant must be told to notify the investigational site about any new medications begun after the start of the study treatment. All medications or nutritional/herbal supplements known to interact with study agent should be excluded. Prohibited medications must be stopped within 2 weeks or 1 half life (whicever is shorter) of investigational agent

administration. If the medication or supplement cannot be discontinued or replaced, the subject should be excluded from this study. Each participant's medication and supplement profile should be reviewed by investigator and/or an oncology trained pharmacist to ensure compliance with this aspect of care. All medications known to interact with the study drug should be avoided after day 18.

5.3.1 INFECTION PROPHYLAXIS AND TREATMENT

In general, participants with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the Investigator for a given infectious condition, according to standard institutional practice.

5.3.2 TRANSFUSIONS OF PLATELETS AND RED BLOOD CELLS (RBC)

Blood, plasma, platelet or red blood cell transfusions are permitted as medically necessary per institutional guidelines. The decision for platelet or red blood cell transfusions should be done in collaboration with study investigator and participant's treating physician. The occurrence of any transfusion occurring prior to end of treatment visit on Day 14 (± 4 days) should be recorded in (e)CRF. Abnormal, clinically significant bleeding may be managed at the discretion of the physician. Antifibrinolytic agents such as transexamic acid may be used in the event of major bleeding events, and bleeding refractory to this may be managed with recombinant factor VIIa (Novo7) or prothrombin complex concentrates, at the discretion of the treating physician and in consultation with study PI.

5.3.3 ANTI-PLATELET AGENTS AND ANTICOAGULANTS

Anti-platelet agents and anticoagulants are permitted only as medically necessary, in case of new thrombosis, and managed per institutional guidelines. Standard of care anticoagulation may be started at any time in conjunction with xisomab 3G3 if deemed warranted by the treating physician. Anti-platelet agents and/or anticoagulants may not be given prior to administration of xisomab 3G3. The decision regarding use of antithrombotics should be done in collaboration with study investigator and participant's treating physician. Participants should be carefully monitored for bleeding risks. The use of any anti-platelet agents or anticoagulants occurring prior to end of treatment visit should be recorded in (e)CRF.

5.3.4 ALLERGIC/HYPERSENSITIVTY REACTIONS

'Allergic/hypersensitivity reactions' or *'cytokine release syndrome/acute infusion reaction'*, per CTCAE v5.0, are defined as AEs related to xisomab 3G3 with onset typically within hours from the start of the study drug infusion. Symptoms should be managed per institutional guidelines as appropriate (e.g., antihistamines, corticosteroids, NSAIDs, and IV fluids).

5.3.5 CONTRACEPTION

The study agent described within this protocol may have adverse effects on a fetus in utero. Non-pregnant, non-breast-feeding women of child-bearing potential may be enrolled if they are willing to use adequate methods of birth control (Refer to Appendix B) or are considered highly unlikely to conceive.

Highly unlikely to conceive women are defined as:

1. Surgically sterilized, or
2. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:
    a. Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
    b. Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).
3. Not heterosexually active for the duration of the study.

Participants should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study individuals must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in Section 7.6. If there is any question that a participant will not reliably comply with the requirements for contraception, they should not be entered into the study.

5.3.6 USE IN PREGNANCY

If a participant inadvertently becomes pregnant while on treatment with study agent, the study site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The pregnancy will be recorded on the (e)CRF and reported by the Investigator to the IRB (refer to Section 7.6.4).

5.3.7 USE IN NURSING WOMEN

It is unknown whether study agent is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, participants who are breast-feeding are not eligible for enrollment.

5.4 PRECAUTIONARY AND PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

Antithrombotic agents (Warfarin, heparin products, direct oral anticoagulants) should be avoided while on study (except for standard of care heparin/tPA flushes if required for catheter maintenance/occlusion). Elective invasive procedures should be delayed until completion of the initial 18 day drug efficacy evaluation period.

5.4.1 BLOOD DONATION

Participants must not donate blood during treatment with study drug and for 1 month following initial administration.

6. STUDY PROCEDURES/EVALUATIONS AND SCHEDULE OF EVENTS

All study visits and laboratory procedures, where possible, should be conducted as part of scheduled standard of care visits.

6.1 **STUDY SPECIFIC PROCEDURES**

6.1.1 MEDICAL HISTORY

A medical history will be obtained by the investigator or qualified designee. In addition to collecting information on demographics, the medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the participant's cancer will be recorded separately and not listed as medical history.

6.1.2 DISEASE ASSESSMENT

The Investigator or qualified designee will obtain prior and current details regarding the participant's cancer.

6.1.3 MEDICATION HISTORY

A complete medication history will be acquired concurrent with medical history.

6.1.4 PHYSICAL EXAMINATION

Physical exams must be performed by a medically qualified individual such as a licensed physician, Physician's Assistant or advanced Registered Nurse Practitioner as local law permits. The physical exam at baseline should include a complete physical exam per institutional standards. All other physical exams after baseline will include an evaluation of any AEs, or any previously reported symptoms, or prior physical examination findings.

A physical examination may include evaluating: weight, general appearance, head, ears, eyes, nose, throat, neck, skin, cardiovascular system, respiratory system, gastrointestinal system, and nervous system. For the purposes of assessing CAT, physical exam should include assessment of participant arm pain and swelling or erythema in the same arm as the catheter.

A physical exam to be conducted: as part of screening visit; within 24hrs or day of single dose of study treatment; and at EOT. If screening visit occurs within 24hrs of study treatment administration, provider visit does not need to be repeated. All physical examinations will also include:

6.1.4.1 *Vital signs*

Vitals to be collected include BP, HR, temperature, and oxygen saturation by pulse oximetry. Unless noted otherwise, vitals will be obtained during each study visit incorporating a physical exam. Significant findings that were present prior to the signature of the informed consent must be included in the Medical History (e)CRF page. Significant new findings that begin or worsen after beginning study treatment must be recorded on the Adverse Event (e)CRF page.

6.1.4.2 *Performance status*

Unless noted otherwise, ECOG status (per Appendix A) will be obtained during each study visit incorporating a physical exam.

6.1.5 HEIGHT AND WEIGHT

Weight must be collected on the day of enrollment.

6.1.6 CATHETER PLACEMENT

Placement of the PICC in participants will be performed according to institutional guidelines. Ultrasound may be used to guide the placement of the PICC, and may include use of local anesthetic. The specific type of PICC (e.g., single or double lumen, brand) will be determined by participants' treatment management team based on needs of their planned anticancer therapy.

Placement of indwelling central venous catheters in participants will be performed according to institutional guidelines. Ultrasound may be used to guide the placement of the indwelling catheter and may include use of local anesthetic. The specific type of indwelling catheter will be determined by participants' treatment management team based on needs of their planned anticancer therapy.

6.1.7 RADIOGRAPHIC IMAGING ASSESSMENTS

All diagnostic and treatment-associated imaging (e.g., MRI, CT, PET) will be performed as clinically indicated in accordance with institutional standards for managing a participant's cancer. Per institutional standards, the use of additional imaging modalities such as the use of contrast venography for assessing CAT or lumen patency is also permitted as clinically indicated. Findings from these studies may be collected.

6.1.8 ULTRASOUND

Per institutional standards, catheters are evaluated for possible CAT via venous duplex ultrasonography 14 (±4) days from time of catheter placement (which will be ±2 days from administration of study agent). Venous duplex ultrasonagraphy to occur as part of EOT visit, prior to provider visit. Assessment will include compression imaging of all the accessible portions of the internal jugular, innominate, subclavian, axillary, cephalic and basilic veins, as well as color Doppler of the internal jugular, subclavian and axillary veins. VTE will be diagnosed based on non-compressibility of a vein segment and/or abnormal color Doppler patterns. Whether the presence of CAT in a participant is symptomatic or asymptomatic at time of ultrasound evaluation will be noted in CRF as part of assessment.

6.1.9 ADVERSE EVENT EVALUATION

Toxicities and adverse experiences will be assessed at each visit using the CTCAE v5.0. Safety will be monitored by assessing physical examination, vital signs, and weight, performance status, hematology, chemistry, coagulation, and pregnancy, as well as collecting of the AEs and medications at study visits.

Adverse events will be monitored from the time the participant signs the informed consent form, but will not be included for analysis if occurring before the study agent is given. Participants will be instructed to report all AEs during the study and will be assessed for the occurrence of AEs throughout the study. All AEs (serious and non-serious) must be recorded in the medical record and (e)CRFs regardless of the assumption of a causal relationship with the study drug; however, known AEs associated with a participant's planned anticancer treatment regimen will not be collected except for the development of grade 3-4 thrombocytopenia. For details on AE collection and reporting, refer to Section 7, Safety.

6.1.9.1 *Assessment of Major and Clinically Relevant Non-major Bleeding*

Bleeding will be defined using the International Society of Thrombosis and Hemostasis definition of major bleeding for clinical investigations of anti-hemostatic medicinal products in nonsurgical patients (i.e., fatal bleeding, critical organ bleeding such as CNS bleeding, or bleeding causing a fall in hemoglobin of 20 g/L or more) and clinically relevant non-major bleeding (i.e., bleeding that does not fit the former definition of major bleeding but prompts medical attention).[27]

6.2 LABORATORY PROCEDURES AND EVALUATIONS

All laboratory procedures and evaluations will occur at times indicated in Section 6.9, Schedule of Events.

6.2.1 HEMATOLOGY

A complete blood count (CBC) with differential will be collected, per institutional standards, and should include : RBC, hematocrit, hemoglobin, platelet, white blood cell (WBC), and WBC differential.

6.2.2 BIOCHEMISTRY

Comprehensive metabolic panel (CMP), including: Na, K, Cl, CO_2, BUN, Creatinine, Ca, Glucose, Albumin, Total protein Alkaline Phosphatase, total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT).

6.2.3 COAGULATION PANEL

Activated Partial Thromboplastin Time (aPTT) and pro-thrombin time (INR) are required at screening (baseline) and on Day 14 (±4 days) study visit. Results from any other coagulation test performed as clinically indicated will also be captured.

6.2.4 ECHOCARDIOGRAM

Required only as clinically indicated.

6.2.5 PREGNANCY TEST

For women of childbearing potential, a serum or urine pregnancy test will be done within 72 hours prior to receiving study drug. If the urine pregnancy test is positive, a serum pregnancy test must be performed per institutional standards.

6.3 EXPLORATORY STUDIES

Research blood specimens will be collected for additional coagulation studies (e.g., PT/INR, and aPTT) and drug PK evaluation.

i) Collection of Specimens

The research blood draws will occur as noted in Section 6.9, Schedule of Events. The research blood draw should be collected in a blue top (3.2% sodium citrate) tube. Collection of research blood should occur before collection of samples in additive-containing tubes such as the EDTA, heparin, or clot activator tubes.

ii) Transport of Specimens

Within 3 hours from time of collection, whole blood research samples should be transported at room temperature to Shatzel Laboratory:

3303 S Bond Ave, CHH13033,
Portland OR 97239

iii) Handling of Specimen

Whole blood samples should be centrifuged at a speed of 1500g for at least 15 minutes to achieve platelet poor plasma. Plasma is to be transferred into a polypropylene vial being careful to avoid the buffy coat. Specimens can be stored at -70°C until ready for analysis.

iv) Site Performing Studies

Coagulation assays will be performed in the investigator's laboratory.

6.4 SCREENING AND BASELINE ASSESSMENTS

A screening (consultation) visit may occur as part of standard of care. If a participant is eligible for the study after review of key inclusion/exclusion criteria, additional screening and/or baseline visits will be scheduled while staff members are requesting insurance authorization to participate in a clinical trial. The following will be reviewed at initial screening visit:

- Clinical history and physical exam (per standard of care)
- Informed consent obtained and documented

Toxicities which occur prior to the start of treatment will not be subject to analysis. Consent must be obtained before initiation of any clinical screening procedures that are performed solely for the purpose of determining eligibility for this research study. Evaluations performed as part of routine care before informed consent can be utilized as screening evaluations if done within the defined time period.

6.5 ASSESSMENTS DURING TREATMENT

Specific on-study assessments are listed in the Section 6.9, Schedule of Events. Visits should occur on Day 1 and Day 14 (±4 days). The Day 14 (±4 days) visit will include an ultrasound, as well as corresponding history and physical exam. The presence of CAT, either symptomatic or asymptomatic, at time of assessment should be recorded in (e)CRF.

For all other assessments: under certain circumstances (e.g., clinic holiday, inclement weather) scheduled visits may be delayed by no more than 4 days, or may occur earlier than scheduled by no more than 4 days.

6.6 **END OF TREATMENT VISIT**

An end of treatment visit should occur on Day 14 (±4 days) after catheter placement and include assessments listed in Section 6.9, Schedule of Events.

If a participant does not reach the end of treatment due to transition to hospice or death, an end of treatment visit will not be conducted.

6.6.1 EARLY TERMINATION VISIT

Participants should be evaluated within 10 days after terminating participation, or evaluated prior to the initiation of any other off-study interventional therapy. Early termination assessments are listed in the Section 6.9, Schedule of Events.

6.7 **FOLLOW-UP**

Participants with AE(s) that require hospitalization will be followed until resolution or stabilization of the AE. Participants will be followed until 60 days from date of catheter placement, initiation of off-study anticoagulation treatment, or death, whichever occurs first (see Section 6.9, Schedule of Events). 60 day follow-up can be performed by phone or chart review.

6.8 **UNSCHEDULED VISITS**

Unscheduled study visits may occur at any time if medically warranted. Any assessments performed (e.g., laboratory or clinical assessments) at those visits should be recorded in (e)CRF.

6.9 SCHEDULE OF EVENTS

Visit Days*	Screening**	On-Study Treatment	End of Treatment Visit	Follow-Up
	Days -28 to -3	Day 1	Day 14 (±4 days)	Day 60 (±4 days)
Informed consent	X			
Inclusion/exclusion criteria	X			
Catheter placement[A]		X		
Xisomab 3G3		X		
Medical history	X			
Medication history	X			
Physical Examination[C]	X	X[G]	X	
Radiographic Imaging	Per investigator's discretion, as clinically indicated			
Ultrasound[D]			X	
Hematology	X			
Biochemistry	X			
Coagulation	X		X	
Pregnancy test[E]	X			
AE assessment and Conmeds[B,F]	X	X	X	X
Research blood draw/Assessment for Immunogenicity[H]	X	X	X	
Electrocardiogram[I]	X	As clinically indicated		

* Ideally the clinic visit and all the study requirements should be performed as indicated.

** Enrolled participants will receive a single fixed dose of xisomab 3G3 (2 mg/kg) through a peripheral IV or the inserted catheter within 48 hours of catheter placement (i.e. ± 2 days). If Xisomab 3G3 is administered prior to D1 catheter placement, eligibility must be confirmed prior to study drug administration.

[A] Placement of the catheter in participants will be performed according to institutional guidelines. Ultrasound may be used to guide the placement of the catheter, and may include use of local anesthetic.

[B] For concomitant medications – enter new medications started during the trial through the end of treatment visit.

[C] All physical exams will include assessing vital signs, weight and ECOG performance status.

[D] Per institutional standards, study participants will be evaluated for CAT via planned ultrasound 14 ±4 days after catheter insertion. Additional ultrasound evaluations may occur at any time during the study based on treating physician and PI discretion; however, only ultrasounds performed within 18 days from catheter placement will be included when computing CAT incidence. Ultrasound to occur as part of EOT, prior to provider visit.

[E] For women of reproductive potential, a serum pregnancy test should be performed within 3 days prior to first dose of trial treatment. Serum pregnancy test should be performed by the local study site laboratory per institutional guidelines, and repeated if required.

Visit Days*	Screening**	On-Study Treatment	End of Treatment Visit	Follow-Up
	Days -28 to -3	Day 1	Day 14 (±4 days)	Day 60 (±4 days)

[F] AEs and laboratory safety measurements will be graded per NCI CTCAE version 5.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness. Report grade 3 and 4 hematological and non-hematological SAEs (related and unrelated to trial treatment) occurring up until 60 days after catheter placement. AE evaluation includes assessment of major and clinically-relevant non-major bleeding per Section 6.1.9.1.

[G]Study visit to occur within 24hrs or day of single dose of study treatment. If screening visit occurs within 24hrs of study treatment administration, D1 provider visit does not need to be repeated.

[H]Blood will be collected and batched on day 14 for Immunogenicity assessment. The Day 1 blood draw should be obtained any time prior to study drug administration.

[I]Electrocardiogram will be obtained at screening and as clinically indiciated.

7. SAFETY

7.1 SPECIFICATION OF SAFETY PARAMETERS

The Investigator is responsible for monitoring the safety of participants who have enrolled in the study. Safety assessments will be based on medical review of adverse events and the results of safety evaluations at specified time points as described in Section 6.9, Schedule of Events. Any clinically significant adverse events persisting at the end of treatment visit will be followed by the Investigator until resolution/stabilization or death, whichever comes first.

7.2 DEFINITIONS

7.2.1 ADVERSE EVENT (AE)

An adverse event is defined as any undesirable physical, psychological or behavioral effect experienced by a participant before and during their participation in an investigational study, in conjunction with the use of the investigational product, whether or not considered intervention-related (21 CFR 312.32 (a)). In general, this includes signs or symptoms experienced by the participant from the time of signing the informed consent to completion of the study.

AEs may include, but are not limited to:

- Subjective or objective symptoms spontaneously offered by the participant and/or observed by the Investigator or medical staff.
- Clinically significant laboratory abnormalities.
- A significant worsening of the participant's condition from study entry.
- Disease signs and symptoms and/or laboratory abnormalities existing prior to the use of the study treatment that resolve but then recur after treatment.
- Disease signs and symptoms and/or laboratory abnormalities existing prior to the use of the study treatment which increase in frequency, intensity, or a change in quality after treatment.

7.2.2 SERIOUS ADVERSE EVENT (SAE)

An AE or suspected adverse reaction is considered "serious" if, in the view of the Investigator, it results in any of the following outcomes:

- Death,
- A life-threatening adverse event,
- In-patient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and/or participant may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include:

- Allergic bronchospasm requiring intensive treatment in an emergency room or at home,
- Blood dyscrasias or convulsions that do not result in in-patient hospitalization, or
- The development of drug dependency or drug abuse.

7.2.3 UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers UPs involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

1. Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
2. Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

This study will use the OHRP definition of UP.

7.2.4 SEVERITY OF EVENT

The Investigator will grade the severity of each AE using, when applicable, the current version of the CTCAE v5.0. In the event of an AE for which no grading scale exists, the Investigator will classify the AE as defined below:

- **Grade 1** – Mild; asymptomatic or mild symptoms, or clinical or diagnostic observations only; intervention not indicated.
- **Grade 2** – Moderate; minimal, local or noninvasive intervention indicated, or limiting age-appropriate instrumental activities of daily living (ADL)
- **Grade 3** – Severe or medically significant but not immediately life-threatening, or hospitalization or prolongation of hospitalization indicated, or disabling, or limiting self-care ADL.
- **Grade 4** – Life-threatening consequences, or urgent intervention indicated.
- **Grade 5** – Death related to AE.

7.2.5 ASSESSMENT OF CAUSALITY RELATIONSHIP TO STUDY AGENT

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and their clinical judgment. The degree of certainty about causality will be graded using the categories below.

- *Definite* – The AE is clearly related to the study treatment.
- *Possible* – The AE may be related to the study treatment.
- *Unrelated* –The AE is clearly NOT related to the study treatment.

7.3 **EXPECTEDNESS**

The Sponsor-investigator will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

7.4 ADVERSE EVENT LIST

7.4.1 ADVERSE EVENT LIST FOR XISOMAB 3G3

Detailed information about the risks and expected AEs of xisomab 3G3 may be found in the current edition of the manufacturer's investigator brochure. In brief, 10 (48%) of 21 subjects experienced a total of 20 treatment emergent adverse events (TEAEs), of which 7 (44%) of 16 subjects received xisomab 3G3 and 3 (60%) of 5 subjects were exposed to placebo. A total of 3 (19%) subjects receiving xisomab 3G3 experienced 5 events that were suspected to be possibly treatment-related by the PI. The highest incidence of TEAEs by organ system was skin and subcutaneous tissue disorders, experienced by 3 (19%) xisomab 3G3-treated subjects and 1 (20%) placebo subject. The most common TEAE in this study was productive cough, experienced by 2 (13%) xisomab 3G3-treated subjects. All other TEAEs were experienced by 1 subject each. The majority of events (17) were mild (Grade 1) in severity and 3 were moderate (Grade 2). Moderate events included increased diastolic BP, productive cough, and upper respiratory tract infection.

7.5 ADVERSE EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an UP, AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF, except for AEs definitely attributable to participant's planned anti-cancer treatment regimen. Information to be collected includes event description, time of onset, clinician's assessment of severity, seriousness, expectedness, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and date of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode. At each study visit, the Investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

The Investigator will record all reportable events with start dates occurring any time after informed consent is obtained until 60 days post study agent dose or until the participant receives alternative anticoagulant therapy, whichever occurs first. Any SAE that occurs after treatment with alternative anticoagulant therapy will be reported only if the Investigator or current treating physician has assessed the SAE as related to the study treatment. Adverse events will be evaluated using the current version of the CTCAE v5.0.

7.6 REPORTING PROCEDURES

7.6.1 OHSU IRB REPORTING OF UNANTICIPATED PROBLEMS AND ADVERSE EVENTS

Unanticipated Problems and AEs will be reported to OHSU IRB according to the policies, procedures and guidelines posted on the OHSU IRB web site.

Per regulatory requirements, if an event is assessed by the Sponsor Institution as a Serious Unexpected Adverse Reaction (SUSAR), it is the responsibility of the Sponsor Institution to submit the SUSAR to Regulatory Authorities according to applicable regulations. In addition, the SUSAR will be distributed to the Investigators/sites utilizing a Council for International Organizations of Medical Sciences (CIOMS) report form, or the MedWatch 3500A form). The Investigator/site will submit a copy of the report to their respective IRB or IEC per the governing institutional requirements and in compliance with local laws and guidelines.

Events that must be reported by the Investigator to the IRB are detailed in the OHSU IRB **Investigator Guidance: Prompt Reporting Requirements (HRP-801)**. At a minimum, events requiring reporting to the IRB include:

- Any new or increased risk related to the research, including AEs or IND safety reports that require a change to the protocol or consent,
- New FDA black box warning,
- Publications identifying new risks,
- Data Safety Monitoring Board/Committee letters recommending changes or discussing new risks
- Unanticipated adverse device effect
- Unauthorized disclosure of confidential participant information

7.6.2 MEDWATCH REPORTING

The Sponsor is required to report AEs to the FDA through the MedWatch reporting program, even if the trial involves a commercially available agent. Adverse events to be reported include any UPs (i.e., not listed in the package insert) and any SAEs with a suspected association to the investigational product.

Adverse events that occur during clinical studies are to be reported to FDA as specified in the investigational new drug/biologic regulations using Form FDA 3500, the MedWatch Voluntary Reporting form (available here), or completed online. A copy of Form FDA 3500 and supporting materials will be kept on file in the study regulatory binder.

7.6.3 ADDITIONAL REPORTING REQUIREMENTS

Unexpected fatal or life-threatening experiences associated with the use of the study treatment will be reported to FDA as soon as possible, but in no event later than 7 calendar days after initial receipt of the information. All other serious unexpected experiences associated with the use of the study treatment will be reported to FDA as soon as possible, but in no event later than 15 calendar days after initial receipt of the information. All events reported to the FDA will also be reported to Aronora Inc. within 24 hours of reporting.

7.6.4 REPORTING OF PREGNANCY

To ensure participant safety, each pregnancy in a participant on study treatment must be reported within 24 hours of learning of its occurrence. The investigator must report the event to the IRB or other oversight entity per institutional policies/requirements. The PI will assess the event and report to the manufactuerer and any other entity as warranted.

The pregnancy should be recorded on a CRF and reported by the Investigator to the Aronora Inc. Pregnancy follow-up should be reported using the same form. Any SAE experienced during pregnancy must be reported. If while on study treatment a participant's sexual partner becomes pregnant, the pregnancy and pregnancy outcomes must also be reported as described above. Consent to report information regarding the pregnancy should be obtained from the pregnant individual.

The investigator must follow the pregnancy to determine outcome, including spontaneous, or voluntary termination, details of the birth, and the presence or absence of any birth defets, congenital abnormalities, or any pregnancy- or childbirth0 related and/or newborn complications.

7.7 **STUDY STOPPING RULES**

The overall study will be paused, and appropriate authorities (e.g., IRB, Knight Data and Safety Monitoring Committee) notified if the following events occur:

- Life-threatening grade 4 toxicity attributable to protocol therapy that is unmanageable, or unexpected.
- Death suspected to be related to study agent

8. STATISTICAL CONSIDERATIONS

Refer to Section 2.1, Description of the Study Design for a detailed description of the study design and endpoints.

8.1 ANALYSIS POPULATIONS

An intent to treat (ITT) analysis set consists of all participants who consent and enroll in the trial regardless of whether they are exposed to the study drug. An efficacy analysis set consists of participants who have placement of a catheter, receive xisomab 3G3 within 48 hours of catheter placement, and have at least one CAT assessment (i.e., ultrasound and physical exam) by Day 18 of the study. A safety analysis set consists of all participants who are exposed to the single dose of study drug.

8.2 DESCRIPTION OF STATISTICAL METHODS

8.2.1 GENERAL APPROACH

This is a single arm phase II trial to assess the efficacy of xisomab 3G3 in reducing the incidence of CAT over 18 days after catheter placement. This study will enroll 50 patients with non-leukemic cancer who are to undergo placement of a central venous catheter and who can wait 2 days from xisomab infusion before initiating antineoplastic therapy.

8.2.2 ANALYSIS OF PRIMARY ENDPOINT

Using the efficacy analysis set, the incidence of ultrasound-detected CAT (including both symptomatic and asymptomatic clots) in the first 18 days after catheter insertion will be assessed and reported with a 95% CI. CAT incidence will also be separately estimated for each general catheter type (i.e., PICC vs. indwelling port).

8.2.3 ANALYSIS OF THE SECONDARY ENDPOINTS

The incidence of major or clinically relevant non-major bleeding (defined in Section 6.1.9.1), along with 95% CI, will be assessed using the safety analysis set. The proportion of safety set participants with these bleeding events will also be separately estimated for each catheter type.

The incidence of xisomab 3G3-associated toxicities will be assessed using the safety analysis set. Descriptive statistics of safety will be presented using CTCAE v5.0. All on-study AEs (from time of consent), treatment-related AEx (from time of xisomab infusion), SAEs, and treatment-related SAEs will be tabulated using worst grade per NCI CTCAE v5.0 criteria by system organ class and preferred term. On-study abnormal lab parameters including hematology, chemistry, liver function, and renal function will be summarized using worst grade NCI CTCAE v5.0 criteria.

8.2.4 ANALYSIS OF THE EXPLORATORY ENDPOINTS

Descriptive statistics will be used to present results of coagulation measures (i.e., platelet count, PT/INR, and aPTT), drug PK, and incidence of catheter occlusion requiring medical therapy (specifically, local administration of tPA). The proportion of participants with symptomatic thrombosis by Day 18 and the median (and range) time from xisomab infusion to clot symptoms

will be reported for those (expected few) participants with symptomatic CAT. All exploratory endpoints will additionally be analyzed within each catheter type (i.e., PICC vs. indwelling central venous catheter).

8.3 SAMPLE SIZE, POWER, ACCRUAL RATE AND STUDY DURATION

8.3.1 SAMPLE SIZE AND POWER

Based on the central venous catheter thrombosis rates and other parameters (e.g., population type, thrombosis evaluation period) in prior studies[4,5,7], the sample size calculation makes the assumption of a 60% incidence of ultrasound-confirmed CAT (i.e., both symptomatic and asymptomatic) over 18 days post- catheter placement in cancer patients not treated with xisomab. A sample size of 50 participants, accounting for a 4% efficacy ineligibility rate, is sufficient to provide 80% power to detect a 20 percentage point reduction in the incidence of CAT at a two-sided α of 0.05.

8.4 HANDLING OF MISSING DATA

Every attempt will be made to obtain data at the defined time points as described in the primary and secondary endpoint descriptions (section 2.2) and the schedule of events (section 6.9). If the data are not sufficient to analyze specific endpoints, the participant's data may be excluded entirely or partially, depending on the specific endpoints in question and in consultation with the biostatistician. No missing data will be imputed. Whenever possible, all available data will be included in the analysis. A sample size for each analysis will be clearly stated along with the reason for exclusion, if any participant is excluded from the analysis due to missing data.

9. CLINICAL MONITORING

9.1 OHSU KNIGHT CANCER INSTITUTE DATA & SAFETY MONITORING PLAN

This study is under the oversight of the Knight Cancer Institute's Data Safety and Monitoring Committee (DSMC) as described in the Knight's institutional Data and Safety Monitoring Plan (DSMP). The Knight DSMP outlines the elements required to ensure the safety of clinical trial participants, the accuracy and integrity of the data and the appropriate modification of cancer-related clinical trials for which significant benefits or risks have been discovered or when the clinical trial cannot be successfully concluded. The Knight DSMP also describes the methods and procedures for ensuring adequate oversight of cancer-related research at OHSU.

As described in the Knight DSMP, regardless of a trial's risk level and any specific Knight oversight in place, the Investigator is singularly responsible for overseeing every aspect of the design, conduct, and final analysis of his/her investigation.

The Knight DSMC reviews and monitors study progress, toxicity, safety, and other data for this study. The DSMC will address any issue that raises questions about data integrity or trial participant safety with the Investigator and study team. Should any major concern arise, the Knight DSMC may recommend corrective action, and determine whether to suspend or terminate the study.

The Knight DSMC evaluates each protocol to determine the risk profile of the trial design. This assessment establishes trial reporting requirements commensurate with risk, and also directs the scope and frequency of Quality Assurance audits. The DSMC may adapt report and audit requirements at any time, if indicated (refer to the Knight DSMP for additional details on reporting and audit frequency). The Investigator will submit trial-specific data reports for the DSMC to assess toxicity and safety data; the report must provide the DSMC with such information as: up-to-date participant accrual; treatment regimen information; current dose level information; AEs and SAEs reported by category; summary of any death on study; unexpected AEs that have been reported; AEs of special or clinical interest; deviations from the approved protocol; that have been reported eligibility exceptions; any inspection, audit, or monitor report; publications and/or developments that may affect scientific validity, subject safety or the ethics of the trial, and a summary of trial status. The study team will provide other information (e.g. scans, laboratory values) upon request.

9.2 CLINICAL DATA & SAFETY MONITORING

As part of the Quality Assurance plan and in full agreement with NIH policy that states all clinical trials require monitoring to ensure the safety of study participants and the validity and integrity of the data, monitoring will be a continuous, ongoing and multifaceted process. This includes external review by the DSMC and IRBs, as well as internal data quality control, review and evaluation. Site monitoring visits are central to this process, and will include reporting to appropriate individuals with oversight responsibilities.STUDY MONITORING REQUIREMENTS The Investigator is responsible for ensuring that the study is conducted in accordance with the protocol, Declaration of Helsinki, GCP, and applicable regulatory requirements, and that valid data are entered into the (e)CRFs. To achieve this objective, the monitor's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized and easily retrievable data. Monitoring visits will be performed during the study to

ensure that the rights and well-being of human participants are protected, that the reported trial data are accurate, and that the conduct of the trial is in compliance with the protocol, GCP, and applicable regulatory requirements.

Details of monitoring activities, including designation of assigned monitoring entities, scope of monitoring visits, timing, frequency, duration of visits, and visit reporting, will be included in a separate Trial-Specific Monitoring Plan (TSMP).

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. The Investigator agrees that the monitor will be permitted to conduct monitoring visits at appropriate intervals. The Investigator agrees to provide all relevant information and documentation as requested by the monitor, including access to all original study documents and source data, including access to electronic medical records and/or source documents if necessary. The Investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

The monitor will conduct source data review and verification as outlined in the TSMP, and following each visit will generate a report summarizing the visit findings.

Regardless of monitoring entity, the OHSU Sponsor-investigator is ultimately, singularly responsible for overseeing every aspect of the design, conduct, and final analysis of this investigation and for governing trial conduct at all participating sites.

If at any time Investigator noncompliance is discovered at OHSU or any participating site, the Sponsor-investigator shall promptly either secure compliance or end the Investigator's participation in the study.

Independent audits may be conducted by the Knight DSMC to verify that the rights and well-being of human participants are protected, that the reported trial data are accurate, that the conduct of the trial is in compliance with the protocol and applicable regulatory requirements, that monitoring practices are adequate and in compliance with the monitoring plan, and that evidence of ongoing investigator oversight is present.

9.3 QUALITY ASSURANCE & QUALITY CONTROL

The investigational site will provide direct access to all trial related source data/documents, and reports for the purpose of monitoring by the monitor and/or sponsor, and auditing by the Knight DSMC and/or regulatory authorities.

All clinical trials at the Knight are required to have a DSMP. All clinical work conducted under this protocol is subject to ICH GCP guidelines. This includes inspection of study-related records by the lead site, sponsor, its designee, or health authority representatives at any time.

Quality assurance (QA) audit activities will occur as detailed in the Knight institutional DSMP. All discrepancies, queries, deviations, observations, and findings of non-compliance will be compiled into a final audit report. The PI must review and assess each finding, and generate a response to the audit report that incorporates a Corrective and Preventative Action (CAPA) plan. The CAPA must analyze root cause(s) of noncompliance to determine the appropriate

changes to correct and resolve issues, and prevent recurrence.

Quality Control (QC) activities will occur to monitor and ensure the safety of study participants and the validity and integrity of data. Monitoring will be a continuous, ongoing and multifaceted process. This includes review by the Knight DSMC and IRBs, as well as internal data quality control, review and evaluation. Site monitoring visits are central to this process, and will include reporting to appropriate individuals with oversight responsibilities.

The Sponsor-investigator, or study monitor, will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

10. DATA HANDLING AND MANAGEMENT RESPONSIBILITIES

10.1 SOURCE DATA/DOCUMENTS

The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The Investigator will maintain adequate case histories of study participants, including accurate (e)CRF and source documentation.

10.2 PARTICIPANT & DATA CONFIDENTIALITY

The information obtained during the conduct of this clinical study is confidential, and unless otherwise noted, disclosure to third parties is prohibited. Information contained within this study will be maintained in accordance with applicable laws protecting participant privacy, including the provisions of the Health Insurance Portability and Accountability Act (HIPAA).

Participant confidentiality is strictly held in trust by the participating Investigator(s) and study team. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or manufacturer supplying study product may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and institutional regulations. Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored within the Knight Cancer Institute per OHSU's Information Security Directives. Individual participants and their research data will be identified by a unique coded identifier consisting of numbers. The study data entry and study management systems used by clinical sites and by Knight Cancer Institute research staff will be secured and password protected per OHSU's Information Security Directives. At the end of the study, or after the appropriate period of record retention stated in Section 10.4, all study databases will be de-identified and archived within the Knight Cancer Institute.

10.3 DATA COLLECTION & STORAGE: PRIVACY, CONFIDENTIALITY & SECURITY

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Standard institutional practices will be followed as described in the OHSU's Information Security Directives to maintain the confidentiality and security of data collected in this study. Study staff will be trained with regard to these

procedures.

Loss of participant confidentiality is a risk of participation. Efforts will be made to keep study participant identities confidential except as required by law. Participants' samples will be identified by code only. Specifically, each consenting participant will be assigned a unique coded identifier consisting of numbers. This identifier will be associated with the participant throughout the duration of their participation in the trial. The coded identifier will also be used to identify any participant specific samples.

Basic accrual tracking information (demographic, consent, visit information) will be captured in OHSU's electronic clinical information research system (eCRIS), hosted on OHSU secure servers and managed by OHSU's information technology group at their data center in downtown Portland, Oregon. Any additional printed documents containing participant identifiers, such as those from the medical record to confirm eligibility, will be filed in binders and kept in a locked, secure location.

Study outcome data will be captured in electronic case report forms (eCRFs) using an electronic data capture (EDC) system on OHSU secure servers, which facilitates information being stored in a unified format and location. To further preserve confidentiality, PHI in the EDC system will be limited to just birth date and visit dates. The web-accessible EDC system is password protected and encrypted with role-based security, and administered by designated informatics staff within OHSU or Knight Cancer Institute. All users of the database are assigned a unique ID, username, and password and must complete training appropriate to their role before they are authorized to enter, access, and store data in the database.

Data from correlative studies will be entered into the EDC system by study personnel at OHSU. All other electronic data extracts will be stored only on OHSU computers and restricted drives, limited only to study investigators and staff with authorization to access the data. Quality assurance will be conducted as outlined in Section 9.3, Quality Assurance & Quality Control.

10.3.1 FUTURE USE OF STORED SPECIMENS

Each participant who signs consent will be assigned a unique coded identifier consisting of numbers. This identifier will be associated with the participant throughout the duration of their participation in the trial. The coded identifier will be used to identify any participant specific samples. As part of this study, blood samples collected for the purposes of this protocol will be stored until they can be analyzed and will then be destroyed, unless the participant consents to remaining blood samples being stored indefinitely in the Shatzel laboratory and further analyzed to address scientific questions and/or development of biological tests related to coagulation.

10.4 **MAINTENANCE OF RECORDS**

Records and documents pertaining to the conduct of this study, source documents, consent forms, laboratory test results and medication inventory records, must be retained by the Investigator for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indicate, until 2 years after the investigation is discontinued and FDA is notified. It is the responsibility of the sponsor to inform the Investigator when these documents no longer need to be retained.

If the Investigator relocates or for any reason withdraws from the study, the study records must be transferred to an agreed upon designee, such as another institution or another investigator at OHSU. Records must be maintained according to institutional or FDA requirements.

10.5 PUBLICATION AND DATA SHARING POLICY

This study will adhere to the requirements set forth by the ICMJE and FDAAA that requires all clinical trials to be registered in a public trials registry (e.g., ClinicalTrials.gov) prior to participant enrollment.

10.6 DELIVERY OF PROGRESS REPORTS TO STUDY FUNDER

Upon the request of Aronora, Inc., the Institution will submit oral or written reports on the progress of the Study as provided by this protocol. Within one hundred and twenty (120) days following the completion or termination of the study, Institution will furnish Aronora, Inc., with a final report detailing the results of the Study.

11. ETHICS/PROTECTION OF HUMAN PARTICIPANTS

11.1 ETHICAL STANDARD

The Investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Participants of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR 312, and/or the ICH E6.

11.2 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

11.3 INFORMED CONSENT

Written informed consent will be obtained from all participants, or the legally authorized representative of the participant, participating in this trial, as stated in the Informed Consent section of 21 CFR Part 50. Documentation of the consent process and a copy of the signed consent shall be maintained in the participant's medical record.

11.3.1 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreement to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families as appropriate. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The Investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks/benefits of the study, alternatives to participation, and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

11.4 PROTOCOL REVIEW

The protocol and informed consent form for this study must be reviewed and approved in writing by the OHSU Knight Cancer Institute's Clinical Research Review Committee (CRRC) and the appropriate IRB prior to any participant being consented on this study.

11.5 CHANGES TO PROTOCOL

Any modification of this protocol must be documented in the form of a protocol revision or amendment submitted by the Investigator and approved by the CRRC and IRB, before the revision or amendment may be implemented. The only circumstance in which the amendment may be initiated without regulatory approval is for a change necessary to eliminate an apparent and immediate hazard to the participant. In that event, the Investigator must notify the IRB (and FDA if under an IND) within 5 business days after the implementation.

An Investigator who holds an IND application must also notify the FDA of changes to the protocol per 21 CFR 312.

12. REFERENCES

1. Grau, D., Clarivet, B., Lotthé, A., Bommart, S. & Parer, S. Complications with peripherally inserted central catheters (PICCs) used in hospitalized patients and outpatients: a prospective cohort study. *Antimicrobial Resistance and Infection Control* **6**, 18 (2017).
2. Climo, M.*, et al.* Prevalence of the use of central venous access devices within and outside of the intensive care unit: results of a survey among hospitals in the prevention epicenter program of the Centers for Disease Control and Prevention. *Infection control and hospital epidemiology* **24**, 942-945 (2003).
3. Gallieni, M., Pittiruti, M. & Biffi, R. Vascular access in oncology patients. *CA: a cancer journal for clinicians* **58**, 323-346 (2008).
4. Itkin, M.*, et al.* Peripherally inserted central catheter thrombosis--reverse tapered versus nontapered catheters: a randomized controlled study. *Journal of vascular and interventional radiology : JVIR* **25**, 85-91.e81 (2014).
5. Paauw, J.D.*, et al.* The incidence of PICC line-associated thrombosis with and without the use of prophylactic anticoagulants. *JPEN. Journal of parenteral and enteral nutrition* **32**, 443-447 (2008).
6. D'Ambrosio, L., Aglietta, M. & Grignani, G. Anticoagulation for Central Venous Catheters in Patients with Cancer. *New England Journal of Medicine* **371**, 1362-1363 (2014).
7. Monreal, M.*, et al.* Upper extremity deep venous thrombosis in cancer patients with venous access devices--prophylaxis with a low molecular weight heparin (Fragmin). *Thrombosis and haemostasis* **75**, 251-253 (1996).
8. Liu, Y.*, et al.* Peripherally inserted central catheter thrombosis incidence and risk factors in cancer patients: a double-center prospective investigation. *Therapeutics and Clinical Risk Management* **11**, 153-160 (2015).
9. Fletcher, J.J., Stetler, W. & Wilson, T.J. The clinical significance of peripherally inserted central venous catheter-related deep vein thrombosis. *Neurocritical care* **15**, 454-460 (2011).
10. Kearon, C.*, et al.* Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. *Chest* **149**, 315-352 (2016).
11. Schiffer, C.A.*, et al.* Central venous catheter care for the patient with cancer: American Society of Clinical Oncology clinical practice guideline. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **31**, 1357-1370 (2013).
12. Sousa, B.*, et al.* Central venous access in oncology: ESMO Clinical Practice Guidelines†. *Annals of Oncology* **26**, v152-v168 (2015).
13. Baumann Kreuziger, L., Onwuemene, O., Kolesar, E., Crowther, M. & Lim, W. Systematic review of anticoagulant treatment of catheter-related thrombosis. *Thrombosis Research* **136**, 1103-1109 (2015).
14. Jones, M.A.*, et al.* Characterizing resolution of catheter-associated upper extremity deep venous thrombosis. *Journal of vascular surgery* **51**, 108-113 (2010).
15. Mahan, C.E., Holdsworth, M.T., Welch, S.M., Borrego, M. & Spyropoulos, A.C. Deep-vein thrombosis: a United States cost model for a preventable and costly adverse event. *Thrombosis and haemostasis* **106**, 405-415 (2011).
16. Grosse, S.D., Nelson, R.E., Nyarko, K.A., Richardson, L.C. & Raskob, G.E. The economic burden of incident venous thromboembolism in the United States: A review of estimated attributable healthcare costs. *Thromb Res* **137**, 3-10 (2016).
17. Karthaus, M.*, et al.* Dalteparin for prevention of catheter-related complications in cancer patients with central venous catheters: final results of a double-blind, placebo-controlled

phase III trial. *Annals of oncology : official journal of the European Society for Medical Oncology* **17**, 289-296 (2006).
18. Akl, E.A.*, et al.* Anticoagulation for people with cancer and central venous catheters. *The Cochrane database of systematic reviews*, Cd006468 (2014).
19. Sousa, B.*, et al.* Central venous access in oncology: ESMO Clinical Practice Guidelines. *Annals of oncology : official journal of the European Society for Medical Oncology* **26 Suppl 5**, v152-168 (2015).
20. Palta, S., Saroa, R. & Palta, A. Overview of the coagulation system. *Indian Journal of Anaesthesia* **58**, 515-523 (2014).
21. Seligsohn, U. Factor XI deficiency in humans. *Journal of thrombosis and haemostasis : JTH* **7 Suppl 1**, 84-87 (2009).
22. Yau, J.W.*, et al.* Selective depletion of factor XI or factor XII with antisense oligonucleotides attenuates catheter thrombosis in rabbits. *Blood* **123**, 2102-2107 (2014).
23. Yau, J.W.*, et al.* Corn trypsin inhibitor coating attenuates the prothrombotic properties of catheters in vitro and in vivo. *Acta biomaterialia* **8**, 4092-4100 (2012).
24. Larsson, M.*, et al.* A factor XIIa inhibitory antibody provides thromboprotection in extracorporeal circulation without increasing bleeding risk. *Science translational medicine* **6**, 222ra217 (2014).
25. Renne, T., Schmaier, A.H., Nickel, K.F., Blomback, M. & Maas, C. In vivo roles of factor XII. *Blood* **120**, 4296-4303 (2012).
26. Buller, H.R.*, et al.* Factor XI antisense oligonucleotide for prevention of venous thrombosis. *The New England journal of medicine* **372**, 232-240 (2015).
27. Schulman, S. & Kearon, C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *Journal of thrombosis and haemostasis : JTH* **3**, 692-694 (2005).

APPENDIX A: PERFORMANCE STATUS

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of self's needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B: CONTRACEPTION

Females of childbearing potential who are sexually active with a non-sterilized male partner or partners of male participant must use 2 highly effective method of contraception. These include: levonorgestrel-releasing intrauterine system (e.g., Mirena®), copper intrauterine device, and hormonal methods. Appropriate hormonal contraceptives include: Etonogestrel-releasing implants (e.g. Implanon® or Norplant®), ethinylestradiol/etonogestrel-releasing intravaginal devices (e.g. NuvaRing®), medroxyprogesterone injection (e.g., Depo-Provera®), normal and low dose combined oral contraceptive pill, norelgestromin/ethinylestradiol-releasing transdermal system (e.g. Ortho Evra®), progesterone based oral contraceptive pill using desogestrel (NB, Cerazette® is currently the only highly effective progesterone-based)

Non-sterilized male participants, or partners of female participant, must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Abstaining from sexual activity for the total duration of the drug treatment and the drug washout period is an acceptable practice for both female and male participants; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female participant should also refrain from breastfeeding throughout this period.