PROTOCOL AMENDMENT 5

Study Winship 2429

Winship 2429: Randomized Trial of Epsilon Aminocaproic Acid versus Platelet Transfusions for the Prevention of Bleeding in Thrombocytopenic Patients with Hematological Malignancies. (PROBLEMA trial: PRevention Of BLeeding in hEmatological Malignancies with Antifibrinolytic (epsilon aminocaproic acid).

Original Protocol Date:	October 18,2013
Amendment 1 Date:	February 18, 2015
Amendment 2 Date:	April 19, 2015
Amendment 3 Date:	August 25, 2015
Amendment 4 Date:	October 24,2016
Amendment 5 Date:	March 22, 2017
Section:	3.4 Description of Treatment *and* Study Schema
Additional information	count < 10 x10^9/L
Rationale:	Clarified in accordance with the standard of care in our institution that the platelet count threshold for platelet transfusions in the inpatient setting is < 10 x10^9/L

Section:	5.3 Study Duration and End of Treatment
Additional information	Subjects that completed treatment due to platelet count recover to > 30 x 10^9/L on 2 measurements obtained 5 days apart whom developed thrombocytopenia > 30 days of end of study and fulfill the inclusions and exclusion criteria are allowed to be re-enrolled in the study. Subjects without platelet recovery that completed 6 months of treatment are not allowed to be re-enrolled in the study
Rationale:	Clarified that subjects after recover platelet count can be re-enrolled in the study

Section:	6.3.2 Dose Escalation

Original text	Patients randomized to EACA who experience persistent grade ≥ 2 oral bleeding secondary to acute or chronic gingivitis or mucositis who do not respond to chlorhexidine 0.12% oral rinse and antibiotic treatment (including but not limited to penicillin and metronidazole or amoxicillin and clavulanate or ampicillin and sulbactam or clindamycin), will receive platelet transfusions as per standard of care and have the option of increasing the dose of EACA to 1,000 mg three times a day. If the dose of 1,000 mg TID is poorly tolerated, then the EACA will be held and restarted at 1,000 mg BID after resolution of the AEs to < grade 1. Patients randomized to EACA who have persistent cutaneous bruises will receive platelet transfusions as per standard of care and have the option of increasing the dose of EACA to 1,000 mg three times a day. If the dose of 1,000 mg TID is poorly tolerated, then the EACA will be held and restarted at 1,000 mg BID after resolution of the AEs to < grade 1. If bruising continues, patient will be taken off study.
Modified text	Patients randomized to EACA who experience any persistent grade ≥ 2 bleeding including hematuria, will receive platelet transfusions as per standard of care and have the option of increasing the dose of EACA to 1,000 mg three times a day. If the dose of 1,000 mg TID is poorly tolerated, then the EACA will be held and restarted at 1,000 mg BID after resolution of the AEs to < grade 1. If patient experience oral bleeding secondary to acute or chronic gingivitis or mucositis who do not respond to chlorhexidine 0.12% oral rinse and antibiotic treatment (including but not limited to penicillin and metronidazole or amoxicillin and clavulanate or ampicillin and sulbactam or clindamycin), then have the option of increasing the dose of EACA to 1,000 mg three times a day. If the dose of 1,000 mg TID is poorly tolerated, then the EACA will be held and restarted at 1,000 mg BID after resolution of the AEs to < grade 1.
Rationale:	Clarify that dose escalation is allowed for any bleeding grade ≥ 2 instead only for oral and cutaneous bleeding.

Section: Table 3	3.5 Study Schema
Changes	1-Screening period was changed to < 21 days instead of -21 to -1. 2- ±3days was removed from Day 1 3- A foot note was added to clarify that the diary card will be completed by arm B-EACA
Rationale:	Clarification for more efficient data entry and avoid duplication

Consent Changes	Procedures Table 1-Screening period was changed to < 21 days instead of -21 to -1. 2- ±3days was removed from Day 1 3- A foot note was modified in accordance with protocol

Study Title: **Winship 2429: Randomized Trial of Epsilon Aminocaproic Acid versus Platelet Transfusions for the Prevention of Bleeding in Thrombocytopenic Patients with Hematological Malignancies. (PROBLEMA trial: PRevention Of BLeeding in hEmatological Malignancies with Antifibrinolytic (epsilon aminocaproic acid).**

Study Phase: Randomized Phase 2

Principal Investigator: Ana Antun, MD

Co-Investigator: H. Jean Khoury, MD

Product Name: epsilon aminocaproic acid (EACA)

IND Reference Number: 119,487

Sponsor: N/A

Protocol Date: March 22, 2017

Version Number: Version 9.0

PROTOCOL REVISION HISTORY:

Protocol Version Number	**Date**
Version 2.0	July 29, 2013
Version 3.0	August 20, 2013
Version 4.0	October 18, 2013
Version 5.0	February 18, 2015
Version 6.0	April 19, 2015
Version 7.0	August 25, 2015
Version 8.0	October 24, 2016
Version 9.0	March 22, 2017

PROTOCOL SYNOPSIS

Study Treatments	**Epsilon aminocaproic acid vs. standard prophylactic platelet transfusions**
Study Title	**Randomized Trial of Epsilon Aminocaproic Acid versus Platelet Transfusions for the Prevention of Bleeding in Thrombocytopenic Patients with Hematological Malignancies. (PROBLEMA trial: PREvention Of BLeeding in hEmatological Malignancies with Antifibrinolytic (epsilon aminocaproic acid).**
Phase	**Randomized Phase 2**
Eligible Population	**Adult patients with acute or chronic thrombocytopenia in the setting of hematological malignancies**
Summary and Study Rationale	**Compare EACA to standard prophylactic platelet transfusion for the prevention of bleeding in thrombocytopenic patients with hematological malignancies**
Study Design	**prospective, randomized, controlled trial**
Study Endpoints	**The primary endpoint is to compare proportion of patients who develop major (grades 3-4) bleeding in each arm.**
Diagnosis and Main Inclusion Criteria	**Age > 18 with hematological malignancies** **Acute or chronic thrombocytopenia with platelet counts < 20 x 10^9/L**
Number of Patients	**100 patients, 50 patients in each arm**
Duration of Patient Participation	**6 months**
Approximate Duration of Study	**3 years**
Dosage and Administration	**1,000 mg twice a day orally**
Prohibited Medications/treatment	**Hydroxyurea and procoagulant agents including DDAVP, recombinant FVII or prothrombin complex concentrate are prohibited in patients receiving EACA**
Safety Evaluations	**Clinical assessment once weekly during the first 30 days and then monthly for 6 months, CBC and bleeding score twice weekly the first 30 days, and then according to standard of care or at discretion of treating physician.**
Statistical Analysis	***Population Analysis*** **Intention to treat (ITT) population: The ITT population includes all patients who are randomized to the study. Patients will be stratified and analyzed according to the treatment to which they were assigned.** **Safety Population: The safety population includes all patients who have received at least 1 dose of EACA. Patients included in the safety population will be analyzed according to the treatment they received.** **Per-protocol Population: The per-protocol population includes all patients who are randomized, receive at least one dose of study drug, and have no major protocol violations that could be expected to impact response data.** ***Study Endpoints***

	- ***Primary Endpoint:*** **is to compare at the end of the study, the proportion of patients with major bleeding during the study period among patients randomized to receive either EACA or standard of care prophylactic platelet transfusions.** - ***Secondary Endpoint*****s include:** • **proportion of patients with any bleeding during the study period in each arm** • **the total number of units of platelets transfused in each arm at the end of the study** • **Quality of life as measured in each arm before the study and at the end of the study** • **Safety in each arm** ***Sample Size*** **This randomized, open-label phase II study is designed to compare proportion of patient with major bleedings ever noted during the study. Patients will be assigned to receive prophylactic EACA (experimental arm) or prophylactic platelet (standard of care) in a 1:1 fashion. Previous studies suggest that the proportions of patients with major bleeding will be expected to be 8% and 30% in experimental arm and standard of care arm, respectively. With one sided Fisher's exact test, the sample size of 45 patients in each arm will achieve a power of 80% at the significance level of 5% to test whether prophylactic EACA can prevent major bleeding better than the standard of care. After adjusting for a 10% drop out rate, the actual required sample size will be 50 patients per arm. Therefore, the total sample size of the study will be 100 patients.** ***Efficacy Analysis*** - ***Primary Endpoint Analysis*** **will be performed using a one-sided fisher exact test to compare the proportions of patients with major bleeding during the whole study between the two arms. The significance level is set at 0.05. This primary analysis will be based on the ITT population.** - ***Secondary Endpoint Analysis*****: one-sided t-test will be used to compare the total number of any bleeding episode noted during the study between the two arms. Two-sided t-test will be employed to compare the total number of units of platelets transfused at the end of the study between the two arms. Appropriate statistical tests (Chi-square test, t-test, Wilcoxon's rank sum test, etc.) will be conducted to compare the each score of the quality of life between the two arms before the study and at the end of the study, respectively. The change of each score of the quality of**

	life from before the study to the end of the study will also be compared between the two arms. The safety in each arm will be also compared with Fisher's exact test. The analyses of secondary endpoints will be performed on the ITT population and the significance level will be kept at 0.05 for all tests. ***Safety Analysis*** **All patients receiving at least 1 dose of study drug will be considered evaluable for safety. Patients will be analyzed for safety according to the treatment which they received. Listings of laboratory test results will also be generated, and descriptive statistics summarizing the changes in laboratory tests over time will be presented. Exposure to study drug over time will also be summarized. The AE incidence rates, as well as the frequency of occurrence of overall toxicity, categorized by toxicity grades (severity) will be described for each treatment arm and be compared between two arms using two-sided Chi-square test or t-test.** ***Quality of Life Analysis*** **Quality of life and health outcomes measures are being collected using EQ-5D-5L instruments before the study and at the end of the study. Means and medians of raw scores of these questionnaires will be summarized for each treatment group for each domain and be compared between the two arms with t-test or Wilcoxon ranks sum test.** ***Interim Analysis*** Three interim analyses are planned after 11 patients in each arm have been randomized and their results have been obtained. Each interim analysis will focus on the primary endpoint, the proportion of patients with major bleeding ever noted during the study. To maintain an overall Type I error rate of 0.05 (1-sided), an O'Brien Fleming approach will be used which requires a 1-sided p-value < 0.001 at the first interim analysis (at 25% of total sample size). If this boundary is not crossed, then the study will continue and the second interim analysis will be conducted at 50% of the total sample side which requires a 1-sided significance level of 0.004. If this boundary is not crossed at the second interim analysis then, the study will continue and a third interim analysis will be conducted at 75% of the total sample side which requires a 1-sided significance level of 0.019. If this boundary is not crossed, the final primary analysis will be performed after completing 100% of the sample size using a 0.043 one-sided significance level.

TABLE OF CONTENTS

Background

1.1 Thrombocytopenia in Patients with Hematological Malignancies

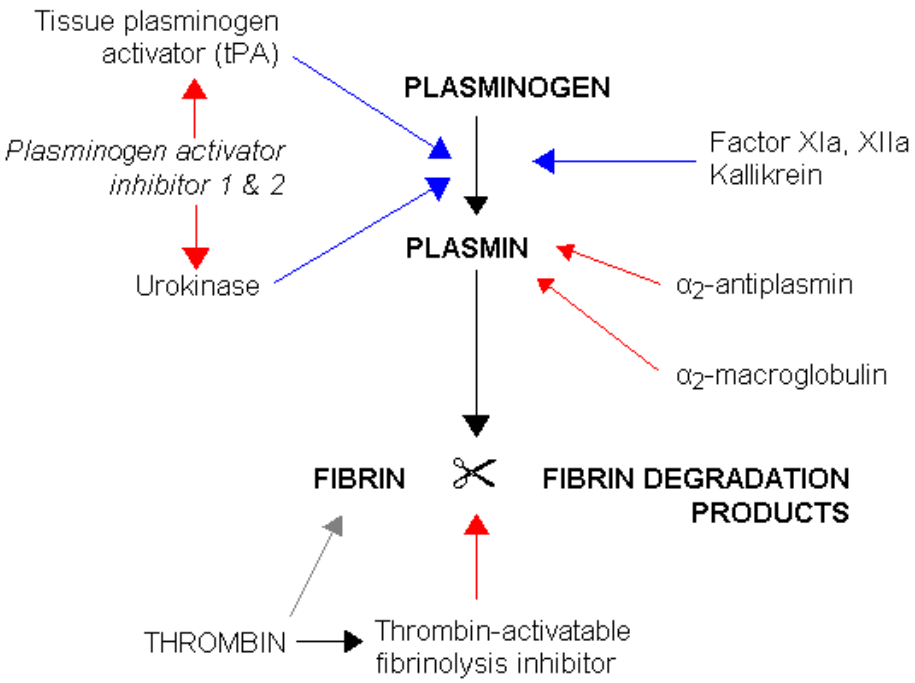
Thrombocytopenia is a very common problem in patient with hematological malignancies and marrow failure syndromes, and is often worsened by the myelosuppressive side-effects of cytotoxic therapies. Despite advances in transfusion medicine and optimization of prophylactic platelet transfusions, **bleeding remains a significant problem in these patients affecting approximately 20% of patients with acute myeloid leukemia and 34-58% of hematopoietic stem cell transplant (HSCT) recipients.** [1] [2]

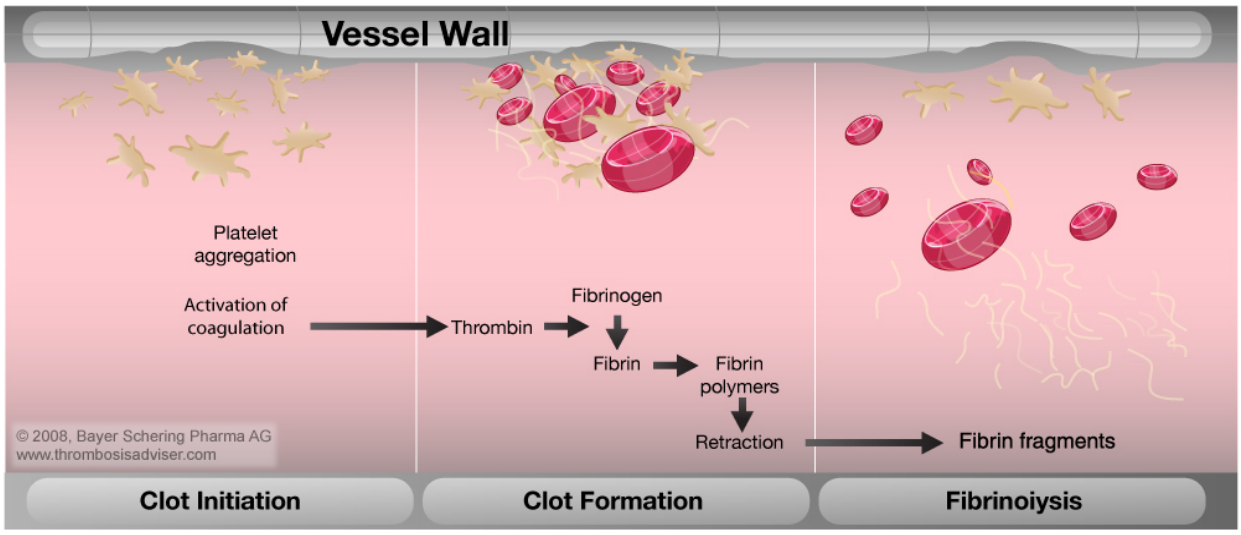
Prophylactic allogeneic platelet transfusion remains the standard of care practice for thrombocytopenic patients. Given the prolonged duration of thrombocytopenia in patients with hematological malignancies, several studies were conducted to identify the lowest safe platelet threshold for transfusion, and the optimal platelet dose. Three randomized trials were conducted in an attempt to identify the lowest safe platelet threshold for platelet transfusion. [3] [4]. Based on the results of these studies, **a platelet count of 10 x 10^9/L is the accepted prophylactic transfusion trigger when patients are hospitalized in the in-patient unit, while 20 x 10^9/L is the accepted threshold for the out-patient.**

Platelet refractoriness is very common in patients with hematological malignancies and marrow failure syndromes. Platelet transfusion refractoriness, defined as a repeated failure to obtain satisfactory response to platelet transfusions or increase in percentage of platelet recovery less than 20-30% at 1 hour post transfusion or 10-20% after 20-24 hour, [5] is a significant problem occurring in 7-34 %. [6] [7] [8] HLA matched platelet transfusions are commonly prescribed in patients with platelet refractoriness; and although effective in some cases, this rather complex, time consuming, and expensive procedure is highly dependent of platelet donor availability. **So maintaining platelet counts in a safe range is practically impossible in these platelet refractory profoundly thrombocytopenic patients due to severe shortening of the platelet survival.**

1.2 Fibrinolysis and Inhibition of Fibrinolysis with Epsilon Aminocaproic Acid (EACA)

1.2.1 ***Fibrinolysis*:** After vessel injury, platelet aggregation and activation of the coagulation cascade pave the way for the generation of thrombin, an essential element for thrombus formation. Thrombin then converts fibrinogen to fibrin, the basic "mesh" that is required for endothelium repair. In order to prevent uncontrolled clot formation, tissue plasminogen activator is released by the endothelium, which then converts plasminogen to plasmin and degrades fibrin into fibrin degradation products. This process, called fibrinolysis is a key element that limits the propagation of intravascular thrombi. (**Figure 1**)





1.2.2 ***Inhibition of Fibrinolysis with EACA:*** EACA is a synthetic monaminocarboxylic acid that effectively inhibits fibrinolysis by preventing the binding of plasmin to fibrin.

- ***Pharmacologic properties of EACA*:** EACA is orally bioavailable, rapidly and completely absorbed from the GI tract, with a peak plasma concentration attained within an hour. Sustained plasma concentration can be maintained by repeated oral dosing or by continuous IV infusion. A plasma concentration of 130 mcg/ml appears necessary to maintain inhibition of systemic fibrinolysis and this plasma concentration reportedly should be attained and sustained by IV

administration of a 5 g loading dose followed by continues IV infusion of 1-1,25 g per hour. The terminal elimination half-life is approximately 2 hours. The 40-45% of a single oral or IV dose is excreted in urine as unchanged drug within 12 hours and approximately 11% is excreted as the metabolite adipic acid. Renal clearance of the drug approximates endogenous creatinine clearance and has been reported to be 116 ml/min. EACA is removed by hemodialysis and may be removed by peritoneal dialysis.

- ***Approved indications for the use of EACA*:** EACA is approved by the FDA for treatment of surgical bleeding complications following heart surgery (with or without cardiac bypass procedures) and portacaval shunt; hematological disorders such as amegakaryocytic thrombocytopenia (accompanying aplastic anemia); acute and life-threatening abruptio placentae; hepatic cirrhosis; and neoplastic disease such as carcinoma of the prostate, lung, stomach, and cervix. Bleeding associated with surgical hematuria (following prostatectomy and nephrectomy) or nonsurgical hematuria (accompanying polycystic or neoplastic diseases of the genitourinary system secondary to urinary fibrinolysis). Platelet dysfunction and von Willebrand, menorrhagia, gastrointestinal tract bleeding, nose and mouth bleeds and coagulation defects such as hemophilia. In the acute bleeding setting, EACA is administered orally or by IV infusion, at an initial dose of 4-5g during the first hour of treatment, followed by 1-1.25g/hour in order to sustain the plasma concentration of the drug at 130 mcg/ml. Maximum dose recommended is 30 g/24 hours. When the bleeding tendency is chronic in nature, a dosage of 5-30g, for 5 days is generally used although lower daily dosage may also be effective.

- ***Side effects associated with the use of EACA and precautions*: Table 1** summarizes side effects reported with the use of EACA. Thrombotic complications are rare with the use of EACA, but have been reported in a patient with hemophilia receiving concomitant therapy with factor IX. EACA may accumulate in patient with decreased renal function, and dose-reduction is recommended. EACA is contraindicated in patients with hematuria originating from the upper urinary tract due to intrarenal obstruction via glomerular capillary thrombosis or clots. In patient receiving long term therapy at doses > 10 g/d, elevations of serum creatine kinase concentrations due to skeletal myopathy were reported.

- ***Contraindications for the use of EACA*:** EACA should not be used when there is evidence of an active intravascular clotting process. EACA must not be used in the presence of disseminated intravascular coagulopathy (DIC) without concomitant heparin.

  In summary EACA is safe and effective therapy that enhances hemostasis in patients with congenital bleeding disorders and bleeding complicating certain medical conditions and surgical procedures.

Table 1. Common Adverse Events reported with the use of EACA and Potential risks [9]

System organ class	Common (>1/100 or <1/10)	Uncommon (>1/1,000 or <1/100)	Rare (>1/10,000 or <1/1,000)	Very Rare <1/10,000	Not known
Blood and lymphatic system disorder		Agranulocytosis, clotting disorders			Leukopenia, thrombocytopenia
Immune System Disorder		Allergic and anaphylactoid reactions, Anaphylaxis			Maculopapular erythema
Nervous System Disorders	dizziness			Confusion, Seizures, Delirium, Hallucinations, Intracranial , Hypertension, Stroke, syncope.	
Eye disorders			Reduce vision, Watery eyes		
Ear and Labyrinth Disorders	Tinnitus				
Cardiac Disorders	Hypotension	Bradycardia	Peripheral ischemia		Thrombosis
Respiratory, Thoracic and mediastinal disorders	Nasal congestion dyspnea	Pulmonary embolism			
Gastrointestinal disorders	Abdominal Pain, Diarrhea, Nausea, Vomiting				
Skin and Subcutaneous tissue disorders		Pruritus, rash			
Musculoskeletal And connective tissue disorders		Muscle Weakness, myalgia	Elevated CPK, Myosis		Acute myopathy, rhabdomyolysis
Renal and Urinary disorders					Renal failure, BUN increased, Nephritic colics and kidney function disorders
Reproductive system and breast disorders					Dry ejaculation
General disorders and administration site conditions	Headache, Malaise, Injection site reaction, Pain and necrosis	Edema			

*frequency not known (cannot be estimated from the available data)

1.3. ***Preliminary Studies***

We analyzed the outcomes of 44 patients with hematological malignancies and marrow failure syndromes who received EACA for the prevention of bleeding, and as a platelet transfusion sparing agent. EACA was given continuously for a median of 47 days, but up to 7 months, at the oral dose of 1 gram twice daily until platelets recovered to > 30 x 10^9/L. Platelets were only transfused in case of bleeding .While on EACA 59% did not bleed, 25% had 19 episodes of spontaneously resolving minor mucocutaneous bleeds for which they did not require platelet transfusion, and 16% received a median of 4 platelet transfusions to treat 1 major traumatic and 9 spontaneous grade 2 –3 bleeding. **Table 2** EACA was well tolerated and venous thrombosis were not observed. EACA was safe, well tolerated and associated with a low risk of major bleeding in chronic severe thrombocytopenic patients with hematological malignancies.

1.4 Rationale for the Conduct of this Study

Given the high incidence of platelet refractoriness, and the prolonged duration of thrombocytopenia in patients with hematological malignancies and marrow failure syndromes, alternatives to platelet transfusions are desperately needed. Our institutional experience with EACA provides a unique expertise to further investigate the role EACA can play in the prevention of bleeding in this patient population. We therefore propose to conduct a prospective, randomized, controlled trial to compare EACA versus standard prophylactic platelet transfusion to prevent bleeding in thrombocytopenic patients with hematological malignancies. The objectives of the trial are to address safety and efficacy of EACA as assessed by major and minor bleeding, cumulative platelet transfusion consumption, quality of life and costs in both arms of the study.

Table 2: Characteristics of 44 thrombocytopenic patients who received epsilon aminocaproic acid for the prevention of bleeding

Age, years median (range)	61 (17-82)
Male/female	29/15
Platelet counts x10^9/L when EACA started, median (range)	8 (1 – 19)
Patients with platelet refractoriness n (%)	10 (23%)
Duration of thrombocytopenia in days, median (range)	273 (20-1463)
Diagnosis n (%) CML AML ALL MDS CLL ITP Lymphomas Aplastic anemia Myelofibrosis	 9 (21) 14 (32) 1 (2) 15 (35) 1 (2) 1 (2) 1 (2) 1 (2) 1 (2)
Disease Status of patients at the time EACA started Active treatment, n (%) Relapsed/refractory, n (%)	 13 (29) 31 (71)
Duration of EACA therapy,median(range) in days	47 (7-209)
Patients without bleeding on EACA, n (%)	26 (59)
Patients with bleeding episodes while on EACA, n (%) Patients requiring platelet transfusions for bleeds, n (%)	18 (41) 7 (16%)
Grade and location of the 10 bleeding episodes requiring platelet transfusions: Grade 4 – CNS*	 1

Grade 3 – rectal Grade 2 – hemorrhoids Grade 2 – hematuria ** Grade 2 – epistaxis Grade 2 – oral Grade 2 – vaginal	1 1 2 1 3 1
Grade and location of the 19 bleeding episodes not requiring platelet transfusions: Grade 1- epistaxis Grade 1 – skin bruises Grade 1 – gingival bleed Grade 1 - vaginal Grade 2 – gingival Grade 2 – vaginal Grade 2 - epistaxis	 7 4 2 1 2 1 2
Reason for discontinuing EACA, n (%) Death Increased platelets count Hematuria	 25 (57) 18 (41) 1 (2)

*Traumatic brain injury in a car accident

**One patient had 2 episodes of hematuria

2 Study Objectives and Hypothesis

2.1. Primary Objective:

The primary objective of this study is to compare the proportion of patients who develop major bleeding episodes (WHO grades 3-4) in the group randomized to receive prophylactic EACA versus standard of care prophylactic platelet transfusions.

2.2 Secondary Objectives:

- To compare the proportion of patients who develop any bleeding episode in the group randomized to receive prophylactic EACA versus standard of care prophylactic platelet transfusions.
- To compare, according to treatment with prophylactic EACA or prophylactic platelet transfusions, the total number of units of platelet transfused
- To compare the quality of life in both arms of the study

2.3 Hypothesis:

This is a non-inferiority trial in which we hypothesize that in thrombocytopenic patients with hematological malignancies, comparable incidence of bleeding will be observed with the prophylactic use of EACA and standard of care arm prophylactic platelet transfusions.

3. Investigational Plan

3.1. Overall Study Design and Plan:

This is a single center, randomized phase 2, open label trial of oral EACA versus platelet transfusions for the prevention of bleeding in thrombocytopenic patients with hematological malignancies.

Eligible patients with acute or chronic thrombocytopenia will be randomized in a 1:1 fashion to receive oral EACA at the dose of 1,000 mg twice daily as a substitute for prophylactic platelet transfusions or standard of care prophylactic platelet transfusions for an untransfused platelet count < 20 $x10^9$/L in the out-patient or in the in-patient setting. Patients will be assessed twice weekly and as needed in between visits for the presence of bleeding. The number of platelets transfused for prophylaxis (arm B) or for therapeutic purposes (both arms) will be monitored. Patients will complete quality of life questionnaire. Adverse events will be assessed and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Bleeding will be assessed and graded according to the World Health Organization (WHO) classification **[Appendix 1].** Patients will be assessed according to a protocol-specific schedule of events. Patients will continue treatment on trial until one or more criteria for discontinuation are met. Patients will be supplied with study drug until they discontinue from the study. Patients will be followed for 2 years or death, whichever occurs first.

3.2. Primary Endpoint:

The primary endpoint is to compare the proportion of patients who develop major bleeding (WHO grade 3 or 4) in each arm.

3.3. Secondary Endpoints:

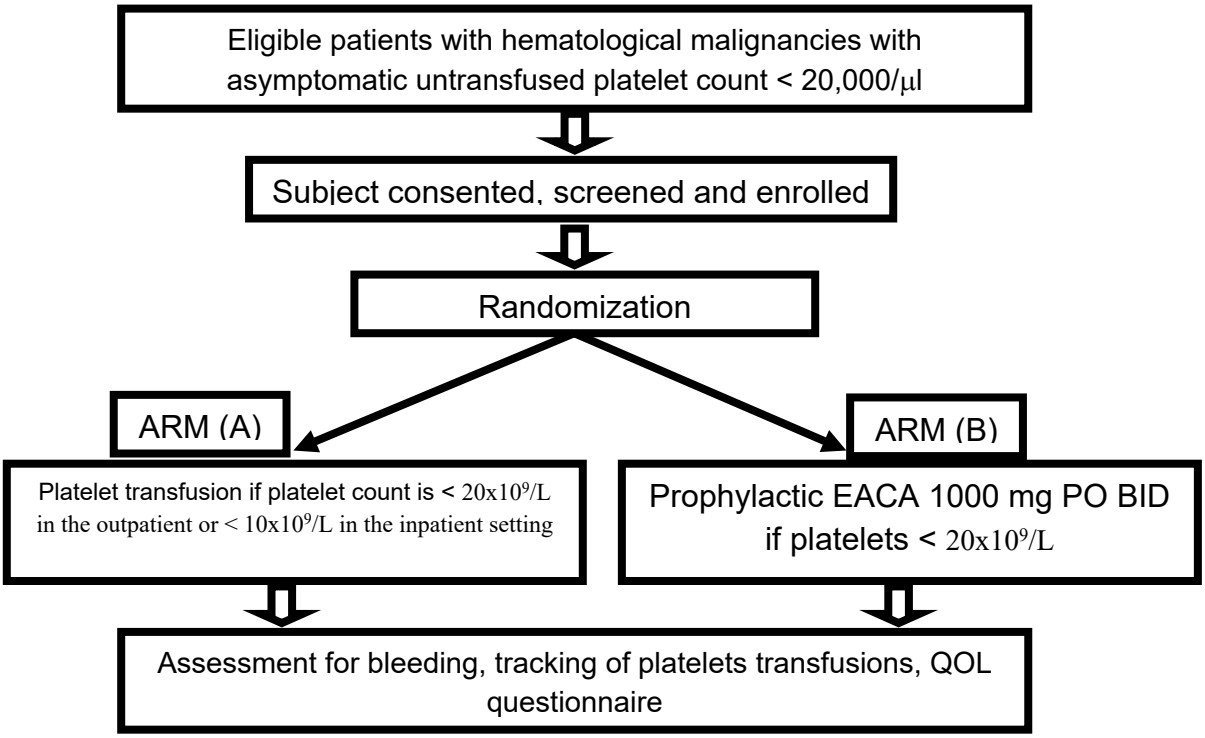
Secondary endpoints include:

- The proportion of patients who develop any bleed in each arm
- The total number of units of platelets transfused in each arm during the study period
- Quality of life as measured by EQ-5D-5L in each arm prior to start treatment and at the end of the study
- Safety in each arm

3.4. Description of Treatment:

Patients will be stratified by expected duration of thrombocytopenia (acute versus chronic), and randomized to receive oral EACA at the dose of 1,000 mg twice daily or the infusion of 1 U of single donor apheresis of platelet when untransfused platelet counts are < 20$x10^9$/L in the out-patient or < 10 $x10^9$/L in the in-patient, as measured on at least twice weekly CBCs (standard of care for cytopenic patients). Schema of the trial is listed in Figure 3.

Study Schema.



3.5. Randomization:

Patients will be randomized on a 1:1 ratio within each strata (acute vs. chronic) to EACA (Arm B) or standard prophylactic platelet transfusions (Arm A) using a standard randomization table. The study is unblinded.

4. **Patient Selection:**

4.1. Inclusion Criteria*:*

- Age > 18 with a hematological malignancy
- Informed consent
- Thrombocytopenia with untransfused platelet counts < 20 x 10^9/L in the out-patient or in the in-patient setting and one of the following criteria:
  1. Acute thrombocytopenia in patients with hematological malignancies who are in remission and are receiving myelosuppressive consolidation chemotherapy that is expected to induce marrow aplasia for at least 2 weeks; or
  2. Acute or chronic thrombocytopenia in patients with acute leukemia (myeloblastic o lymphoblastic) receiving induction or re-induction chemotherapy that is expected to induce marrow aplasia for at least 2 weeks; or Expected chronic thrombocytopenia in patients with newly diagnosed marrow failure syndromes, myelodysplastic syndromes, aplastic anemia, chronic myelomonocytic leukemia or myelofibrosis; or
  3. Expected chronic thrombocytopenia in patients with relapsed or refractory hematological malignancies; or

4. Hematopoietic stem cell transplant recipients with chronic thrombocytopenia due to chronic GVHD or other causes.

4.2 Exclusion Criteria:

- Acute promyelocytic leukemia
- Patient receiving anticoagulation
- Patient receiving antiplatelet agents
- Patient treated with antifibrinolytic agents (including EACA) within 14 days prior to screening.
- Subjects receiving procoagulant agent including DDAVP, recombinant FVII or prothrombin complex concentrate within 24 hours of enrollment
- Subject with known congenital bleeding disorders or platelet dysfunction
- Disseminated intravascular coagulation
- Fibrinogen level < 150 mg/dl
- Patients with known lupus anticoagulant or positive antiphospholipid antibody
- History of arterial or venous thromboembolic disease 6 months prior to screening
- Patient requiring platelet transfusion threshold of > $20x10^9$/L
- Active grade $\geq$ 2 bleeding at the time of randomization, including hematuria
- History of grade 4 bleeding
- Hematopoietic stem cell transplant recipient within 100 days post-transplant
- Pregnancy
- Known allergy to EACA
- History of veno-occlusive disease of the liver
- Myocardial infarction 6 months prior to screening
- Unstable angina
- Grade 2 renal dysfunction: creatinine > 2-3 times the upper limit of normal

5. Study Procedures

5.1 Schedule of Events

Table 3. Screening and study procedures to be done through the end of the study. Evaluation visit samples or activities should occur within 3 days of the scheduled study day

	Screening	**Cycle 1**				**Monthly** (until Month 6)	**End of treatment**
	Day <21	**Day 1**	**Day 8** ±3days	**Day 15** ±3days	**Day 22** ±3days	**Day 1** ±3days	
Informed Consent	**X**						
History and Demographics	**X**						
Hematological disorder diagnosis and prior therapy	**X**						
Urine HCG	**X**						
Vital Signs, ECOG PS and Physical Examination	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Concomitant medications	**X**	**X**	**X**	**X**	**X**	**X**	**X**

Randomization	**X**						
CBC*	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Fibrinogen	**X**						
Comprehensive metabolic panel**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Patient's questionnaire QOL		**X**					**X**
Transfusions records		**X**	**X**	**X**	**X**	**X**	**X**
Diary card***		**X**	**X**	**X**	**X**	**X**	**X**
Bleeding score WHO*	**X**	**X**	**X**	**X**	**X**	**X**	**X**
AE's		**X**	**X**	**X**	**X**	**X**	**X**
SAE		**X**	**X**	**X**	**X**	**X**	**X**

*First 30 days , i.e.: twice weekly or at the discretion of the treating physician, but at least once a week.(If the decision is twice a week, the non-visit day bleeding score may be assessed in person or by phone). After 30 days CBC and bleeding score will be performed according to the standard of care for cytopenic patients **glucose, serum calcium, blood urea nitrogen, creatinine, sodium, potassium, chloride, serum albumin, serum total proteins, carbon dioxide, alkaline phosphatase, aspartate amino transferase and alanine amino transferase. The screening procedures including blood and urine test obtained as part of the routine care, up to 72 hours prior to consenting, may be used to qualify the subject for eligibility and randomization. *** Diary card to be completed by Arm B - EACA

The following describes the procedures/tests required for this study:

Informed Consent: All patients must take part in the informed consent process prior to any study related activity. During the consent process, the person obtaining consent must inform the patient of all elements of informed consent. Adequate time must be allowed for questions and for the patient to make a voluntary decision. No protocol-specific procedures are to be performed until the patient has signed and dated the IRB approved informed consent form. Each patient's participation in the trial begins with the signing and dating of the informed consent form.

Screening: Screening tests and procedures are used to establish eligibility of the patient for the trial. Patients must continue to maintain laboratory values within eligibility parameters if any given procedure or laboratory test is repeated prior to randomization. All screening tests must be done within 7 days prior to randomization.

Randomization: Randomization procedure will be performed following complete eligibility assessments and just prior to the initiation of assigned treatment.

Medical/Surgical History and Demographics: Medical and surgical history and demographic information will be recorded. Medical and surgical history includes diagnoses, therapies, medical and surgical treatments, and current medications. Demographic information consists of the patient's age, gender, race, and ethnicity.

Hematological Disorder Diagnosis: The initial hematological diagnosis including the date of onset of the diagnosis must be recorded.

Vital signs and Physical Examination: Vital signs are temperature, pulse, respiratory rate, and blood pressure. A complete physical examination, including weight, must be performed at screening, prior to the first administration of study drug, and at the End-of-Treatment Visit. All subsequent physical examinations are part of the standard of care but should be directed to relevant bleeding findings in the patient.

Complete Blood Count (CBC): CBC with differential is defined as peripheral blood total white blood cell (WBC) count, hemoglobin, hematocrit, and platelet count. This is a standard of care test obtained routinely in all patients with hematological disorders.

Chemistry (Comprehensive metabolic panel): is a set of 14 chemical test including sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, serum calcium, serum albumin, serum total proteins, carbon dioxide, alkaline phosphatase, aspartate amino transferase and alanine amino transferase

EQ-5D Assessments: The EQ-5D-5L will be used to collect patient-assessed quality of life and health outcomes measures. Patients are required to complete the instruments if there is a validated translation in a language in which they are fluent.

Bleeding score: Bleeding will be graded according with the WHO bleeding scale (Appendix 1) and recorded in the medical records during each visit. For hospitalized subjects enrolled on this trial, bleeding will be described in the daily follow up note by physician, nurse practitioner or physician assistant and graded by the investigator.

End of Treatment or Early Termination Procedures: The End-of-Treatment (or early termination) Visit should be performed within 2 weeks (14 days) of the patient's last dose of study drug or the patient/investigator decision to end treatment, whichever is later.

Follow-up Procedures: Safety: All AEs ongoing or starting within 30 days after the End-of-Treatment must be recorded on the CRF. After this time, ongoing AEs thought to be at least possibly study-drug related and all ongoing SAEs should be followed at least every 4 weeks until they resolve to baseline (or CTCAE grade ≤ 1), stabilize, or are considered to be chronic or irreversible.

Follow-up Procedures: Survival: Survival data will be collected every 12 weeks $\pm$ 2 weeks starting after the last dose of the assigned study treatment or the investigator/patient decision to discontinue treatment, whichever occurs later and continuing for up to 12 months from the time the last patient is randomized to a treatment group. These data do not need to be obtained during a visit; phone contact is acceptable.

5.2 Patient Registration and Identification

Demographic information on all patients who sign the Informed Consent Form will be recorded on the master subject log. Those patients who complete screening procedures and meet all eligible criteria may be enrolled. At the time of enrollment, the patient will be assigned a unique identification code (number), consisting of a study site number and a unique consecutive number.

5.2.1 Screen Failure

Patients who have signed informed consent and subsequently fail to meet the inclusion and/or exclusion criteria are defined as screen failures. For all screen failures, the Investigator is to maintain a screening log that documents the patient initials and reason(s) for screen failure. A copy of the log will be retained in the Investigator's study files. Any patient who is rescreened after screen failure must, in addition to the failed procedure, repeat only those screening procedures outlined in the Schedule of Events that have fallen outside the specified screening period.

5.2.2 Early Discontinuation

In the event that a patient is withdrawn from the study, every effort will be made by the Investigator to document and report the reasons for withdrawal as thoroughly as possible. The reason(s) for termination must be clearly reported on the appropriate page of the patient's CRF. An End-of-Treatment reason for discontinuation must be recorded for any patient who is randomized. If a patient is discontinued from the trial for any reason, every effort must be made to perform all clinical and laboratory procedures as scheduled for the End-of-Treatment Visit. In the event that the patient fails to return for the necessary visit(s), an effort must be made to contact the patient to determine the reason, and this information should be recorded in the appropriate source record and the end-of-treatment CRF.

5.3 Study Duration and End of Treatment

The total estimated duration of the study is up to 3 year, including 14 months to accrue patients with up to 1 year for treatment and follow up for the last patient. Patients will be supplied study drug until they discontinue from the study.

End of treatment is defined when untransfused platelet count recover to > 30 x 10^9/L on 2 measurements obtained 5 days apart. For patients without platelets recovery, end of treatment will be set at 6 months. At that time patients will be taken off treatment and enter a long-term follow-up period for 2 years.

Subjects that completed treatment due to platelet count recover to > 30 x 10^9/L on 2 measurements obtained 5 days apart whom developed thrombocytopenia > 30 days of end of study and fulfill the inclusions and exclusion criteria are allowed to be re-enrolled in the study. Subjects without platelet recovery that completed 6 months of treatment are not allowed to be re-enrolled in the study

5.4 Withdrawal Criteria

- Patients will be discontinued from further study drug administration if any of the following occur: Intolerable toxicity as determined by the Investigator
- Grade 4 bleeding on either arm of this study
- Development on trial of a deep venous thrombosis, pulmonary embolism or cerebrovascular event on either arm of this study
- Grade ≥2 CPK elevation on the EACA arm
- Grade ≥3 myalgia on the EACA arm
- Development on trial of disseminated intravascular coagulation (DIC)
- Development on trial of a condition that requires anticoagulation
- A treatment interruption for study-drug (EACA) related non-hematologic toxicities lasting longer than 28 days
- Significant deviation from the protocol or eligibility criteria
- Noncompliance with study or follow-up procedures
- Pregnancy
- Patient withdrawal of consent and decision to discontinue participation
- Termination of the trial
- Any other reason that, in the opinion of the Investigator, would justify removal of the patient from the study

5.5 Study Termination

If the investigator, Data Monitoring Committee, or regulatory agencies discover conditions during the study that indicate that the study or site should be terminated, this action may be taken after appropriate

consultation between the investigator, and Data Monitoring Committee. Conditions that may warrant termination of the study include, but are not limited to:

- The discovery of a serious, unexpected, or unacceptable risk to subjects enrolled in the study
- Submission of knowingly false information from the research facility to the regulatory authorities
- Insufficient adherence to protocol requirements

Study termination and follow-up will be performed in compliance with the conditions set forth in the guidelines for GCP, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

6. <u>Safety and Quality of Life Assessments</u>

6.1.1 Safety Assessments: Safety will be assessed by routine physical and laboratory evaluations. AEs will be recorded and the severity will be graded according to the NCI CTCAE v.4.0.

6.1.1. Adverse Events: Type, incidence, severity (graded in accordance with the NCI CTCAE v.4.0), timing, seriousness and relatedness, outcome, action taken with study drug, and treatment will be assessed and documented by the investigator continuously throughout the study. Baseline malignancy-related signs and symptoms will be recorded as AEs during the study if they worsen in severity or increase in frequency. Procedures for following AEs at the end of treatment and beyond are outlined in Section 5.1.

6.2. Quality of Life Assessments: Patients will be asked to fill the EQ-5D-5L. The EQ-5D-5L questionnaire is a validated, self-administered general questionnaire of health-related quality of life (HR-QoL) issues, developed by EuroQoL Group. The questionnaire asks patients to rate their HR-QoL for 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The instrument contains a descriptive element, with patients being asked to rate each dimension on a 5-level descriptive severity scale; and a visual analog scale, where the same dimensions are rated along a 100-point visual ruler. Patients for whom a validated translation exists in a language in which they are fluent will complete the EQ-5D-5L during study visits as outlined in the Schedule of Events.

6.3. Study Treatments:Patients will be randomized to receive for bleeding prophylaxis either EACA or prophylactic platelet transfusions. EACA will be self-administered by the patient on a daily schedule.

6.3.1 Dose Selection, Treatment Administration and Compliance

6.3.1.1 EACA

The starting dose of EACA will be 1,000 mg taken orally twice daily. Patients will take the prescribed number of tablets at approximately the same time each day. Patients will be provided a diary card where the date of administration will be recorded. Patients who forget to take their dose more than 6 hours after it is due shall not make up the missed dose. Any missing doses should be recorded, and subsequent training of patients should be documented in the appropriate source record (e.g., clinic chart). The starting dose was selected based on our institutional experience (Section 1.3).

6.3.1.2 Prophylactic Platelet Transfusions

Patients not randomized to the EACA arm with platelet counts < $20x10^9$/L in the out-patient or <$10x10^9$/L in the in-patient will receive a single donor unit of pheresed platelets in the infusion center after pre-medication with acetaminophen and diphenhydramine per institutional guidelines. Documentation of the transfusion will be maintained according to the hospital's Standard Operating Procedures, with documentation of the start and end time of the infusion, as well as adverse events during the infusion and

its management. Platelet refractory patients will receive prophylactic platelet transfusions as described above.

6.3.1.3 Therapeutic Platelet Transfusions

On both arms of the study, patients will receive therapeutic platelets transfusion for any grade ≥ 2 bleeding per standard of care. Platelet refractory patients will receive HLA match platelet transfusions per standard of care.

6.3.2 Dose Escalation

Patients randomized to EACA who experience any persistent grade ≥ 2 bleeding including hematuria, will receive platelet transfusions as per standard of care and have the option of increasing the dose of EACA to 1,000 mg three times a day. If the dose of 1,000 mg TID is poorly tolerated, then the EACA will be held and restarted at 1,000 mg BID after resolution of the AEs to < grade 1.

If patient experience oral bleeding secondary to acute or chronic gingivitis or mucositis who do not respond to chlorhexidine 0.12% oral rinse and antibiotic treatment (including but not limited to penicillin and metronidazole or amoxicillin and clavulanate or ampicillin and sulbactam or clindamycin), then have the option of increasing the dose of EACA to 1,000 mg three times a day. If the dose of 1,000 mg TID is poorly tolerated, then the EACA will be held and restarted at 1,000 mg BID after resolution of the AEs to < grade 1.

Patients randomized to EACA who have persistent cutaneous bruises will receive platelet transfusions as per standard of care and have the option of increasing the dose of EACA to 1,000 mg three times a day. If the dose of 1,000 mg TID is poorly tolerated, then the EACA will be held and restarted at 1,000 mg BID after resolution of the AEs to < grade 1. If bruising continues, patient will be taken off study.

6.3.3 Dose Reduction

Patients randomized to EACA 1000 mg twice a day or higher who experience grade ≥2 toxicity attributable to EACA, will hold the study drug until resolution of the adverse event to < grade 1. EACA will then be reduced by 50%, restarted at 1000 mg daily after the resolution of the AE's to < grade 1

6.4 Allocation of Treatment

The results of screening assessments for each patient will be reviewed by the study PI, who will approve each patient for randomization. Upon this approval, patients will be randomized to treatment with either EACA or standard of care prophylactic platelet transfusions using a standard randomization table.

6.5 Concomitant Medications

All concomitant medications administered from the time of informed consent signature through 30 days after the end of treatment (last dose or investigator/patient decision to discontinue, whichever is later) are to be reported on the appropriate CRF for each patient.

6.5.1 Permitted Medications

All routine and appropriate supportive care (including red blood cell products) will be allowed during this study, as clinically indicated, and in accordance with the standard of care practices. Clinical judgment should be utilized in the treatment of any AE experienced by the patient. Information on all concomitant medications, administered blood products, as well as interventions occurring during the study must be recorded on the patient's CRF.

6.5.2 Prohibited Medications

Hydroxyurea and procoagulant agents including DDAVP, recombinant FVII or prothrombin complex concentrate are prohibited in patients receiving EACA.

6.5.3 Treatment Supply

6.5.3.1 Formulation, Packaging and Labeling

EACA investigational drug product is supplied as tablets. Each tablet contains 500 mg of EACA active ingredient. Tablets will be supplied as follows: 60 count in 30 cc white high density polyethylene (HDPE) bottles with induction-sealed child resistant caps. Bottle labels will bear the appropriate label text as required by governing regulatory agencies, to include product name, product strength, number of tablets, lot number, appropriate temperature range for storage and statement that drug is limited by federal law to investigational use only.

6.5.3.2 Treatment Storage, Dispensing, and Accountability

The recommended storage condition for aminocaproic acid is 25°C. The study pharmacist or designee at the site will be responsible for handling, dispensing study drug, completing associated documentary paperwork, handling dispensing log/accountability form. Each time study medication is dispensed for a patient, the following information be recorded: the patient's initials, the patient's study number, tablet strength, the number of tablets dispensed with the corresponding lot number, and the initials of the person dispensing the drug. These logs are to be maintained by the study pharmacist in the pharmacy throughout the duration of the study. The Investigator is responsible for ensuring that the patient diary card(s) and study drug provided to the patient and returned from the patient are accounted for and noted in source documentation.

6.5.3.2.1 Disposition of used supplies

All used bottles or packs of study drug must be destroyed in an appropriate manner according to the standard practice. Destruction of such supplies will be documented. During the trial and at termination, patients must return all unused study drug supplies and the return of these unused study drug supplies must be recorded. Returned supplies must not be re-dispensed. No other utilization of EACA intended for use in this study will be authorized. The Principal Investigator or his/her designee will be responsible for the appropriate handling and disposition of residual study drug.

7. Adverse Events Reporting

7.1 Adverse Events

7.1.1 Adverse Event Definition

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product whether or not considered related to the medicinal product. Any worsening of a preexisting condition, which is temporally associated with the use of the study drug (i.e., occurs after the first dose of study drug), is also an AE. Adverse events include:

- Abnormal test findings
- Changes in physical exam findings
- Other untoward medical events, regardless of their relationship to the study drug, such as injury, events that require surgery, accidents, or apparently unrelated illnesses, and hypersensitivity
- AEs may include signs or symptoms resulting from: drug overdose, drug withdrawal, drug abuse, drug misuse, drug interactions, drug dependency, and, in utero drug exposure

7.1.2 Abnormal Laboratory Tests

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms that are considered clinically significant in the opinion of the investigator
- Test result requires additional diagnostic testing (other than merely repeating an abnormal test) or medical/surgical intervention
- Test result leads to a change in study drug dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy
- Test result is considered to be an AE by the investigator

7.1.3 Performing Adverse Event Assessment

All observed or volunteered AEs, regardless of treatment group or suspected causal relationship to the investigational product, will be reported as described in the following sections. For all AEs, the investigator must pursue and obtain information adequate to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious AE requiring immediate notification to the appropriate regulatory agencies.

7.1.4 Reporting Period

Serious Unexpected Suspected Adverse Reactions require notification of the appropriate regulatory agencies beginning from the time the patient provides informed consent, which is obtained prior to the patient's participation in the clinical study (ie, prior to undergoing any study-related procedure and/or receiving investigational product), through and including 30 days after the last administration of the assigned study treatment or the investigator/patient decision to discontinue treatment, whichever occurs later. Any SAE occurring any time during the reporting period must be reported to the FDA within 15 days of determining reportability if a causal relationship to the investigational product is suspected. Any SAE ongoing at the end of the reporting period should be followed as described below. For all enrolled patients, AEs (serious and non-serious) should be recorded on the eCRF beginning with the signing of the informed consent form and concluding 30 days following the last dose of the assigned study treatment or the investigator/patient decision to discontinue treatment, whichever occurs later. AEs ongoing after the reporting period: Any ongoing AEs thought to be at least possibly study-drug related and all ongoing SAEs after this time should be followed at least every 4 weeks until they resolve to baseline (or CTCAE grade ≤ 1), stabilize, or are considered to be chronic/irreversible.

7.1.5 Adverse Event Severity

The severity of AEs will be assessed according to the CTCAE, v.4.0. If the AE is not defined in the CTCAE, the investigator will determine the severity of the AE based on the following definitions:

- Mild (grade 1): The AE is noticeable to the patient but does not interfere with routine activity. The AE does not require discontinuing administration or reducing the dose of the study drug
- Moderate (grade 2): The AE interferes with routine activity but responds to symptomatic therapy or rest. The AE may require reducing the dose, but not discontinuing administration of the study drug
- Severe (grade 3): The AE significantly limits the patient's ability to perform routine activities despite symptomatic therapy. In addition, the AE leads to discontinuing administration or reducing the dose of the study drug
- Life-Threatening (grade 4): The AE requires discontinuing administration of the study drug. The patient is at immediate risk of death

- Death (grade 5): The patient dies as a direct result of the complication or condition induced by administration of the study drug

7.1.6 Causality

The investigator's assessment of causality must be provided for all AEs (serious and non-serious). An investigator's causality assessment is the determination of whether exists a reasonable possibility that the investigational product caused or contributed to the AE. In addition, if the investigator determines an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and on the SAE form and report such an assessment in accordance with the SAE reporting requirements. The investigator will use medical consideration and use the following categories of causality to determine the relatedness of an AE with the study drug based on the following definitions. Not all criteria in each category of relatedness must be present.

- Definitely Not Related (not drug related): The patient did not receive study drug, OR the temporal sequence of the AE onset relative to the administration of the study drug is not reasonable, OR there is another obvious cause of the AE
- Probably Not Related (not drug related): there is evidence of exposure to study drug, there is another more likely cause of the AE, dechallenge (if performed) is negative or ambiguous, rechallenge (if performed) is negative or ambiguous
- Possibly Related (drug related): there is evidence of exposure to study drug, the temporal sequence of the AE onset relative to administration of the study drug is reasonable, the AE could have been due to another equally likely cause, dechallenge (if performed) is positive
- Probably Related (drug related): there is evidence of exposure to study drug, the temporal sequence of the AE onset relative to administration of the study drug is reasonable, the AE is more likely explained by the study drug than by another cause
- Definitely Related (drug related): there is evidence of exposure to study drug, the temporal sequence of the AE onset relative to administration of the study drug is reasonable, dechallenge is positive, rechallenge (if feasible) is positive, the AE shows a pattern consistent with previous knowledge of the test drug or a test drug class

7.1.7 Expectedness

The expectedness of an SAE is assessed by the Investigator in the overall classification of SAEs for regulatory reportability. The EACA Investigator's Brochure will be used as the reference for determination of expectedness and risk assessment.

7.2 Serious Adverse Events

The definitions and reporting requirements of ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2A, will be adhered to.

7.2.1 Serious Adverse Event Definition

An AE is considered an SAE if at least one of the following conditions applies:

- Death: An AE that results in death is any patient death within 30 days of the last dose of study drug administration. The cause of death or AE that resulted in a fatal outcome is the SAE
- Life-threatening AE: An AE that places the patient, in the view of the investigator or the sponsor, at immediate risk of death from the event as it occurred (i.e., this does not include an event that had it occurred in a more severe form might have caused death)

- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions: Any substantial disruption of a person's ability to conduct normal life functions
- Inpatient hospitalization or prolongation of existing hospitalization: Hospitalization refers to admission of a patient into a hospital for any length of time
- A congenital anomaly/birth defect: A fixed, permanent impairment established at or before birth
- Cancer: Occurrence or diagnosis of a new cancer during the study is considered an SAE. A new cancer is a cancer that is histopathologically different than the cancer under study in the trial (ie, does not include metastatic or progressive disease)
- Overdose: Occurrences of overdose must be reported as an SAE
- Important medical event: Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not result in death, be life-threatening, or require hospitalization. However, if it is determined that the event may jeopardize the patient and/or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical events should be reported as serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse.

Adverse events (reported from clinical studies) that require hospitalization or prolongation of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a health care facility meets these criteria. Adverse events that require emergency room care that do not result in hospital admission are not SAEs unless assessed by the investigator to be an important medical event. Hospitalization does not include the following: Hospice facilities, Respite care, skilled nursing facilities, Nursing home, Routine emergency room admissions, and same day surgeries (as outpatient/same day/ambulatory procedure)

Hospitalization or prolongation of hospitalization in the absence of a precipitating AE is not in itself an SAE. Examples include: Social admission (eg, patient has no place to sleep), Protocol-specified admission during a clinical study (eg, for a procedure required by the study protocol), Optional admission not associated with a precipitating AE (eg, for elective cosmetic surgery that was planned prior to study enrollment [appropriate documentation is required for these cases]), Hospitalization or prolongation of hospitalization for scheduled therapy of target malignancy of the study is not considered an SAE

7.2.2 Reporting Serious Adverse Events

The investigator or designee must

- Complete a Serious Adverse Event Case Report Form in the subject's study record within 72 hours of recognition.
- Submit events that are a Serious Unexpected Suspected Adverse Reaction to the FDA within 15 calendar days of determining reportablility
- Observe Emory University IRB Unanticipated Problem policy to determine events that meet requirements for immediate reporting. If an event meets the Emory University IRB requirements as an UP, the event will be submitted to the IRB and the DSMB. This timeframe also applies to additional new information (follow-up) on previously forwarded SAEs. Should the FDA or

national regulatory authorities require additional data on the event; the sponsor-investigator will ensure that those data are provided to the appropriate regulatory agencies in a timely fashion.

The following information about the patient and the event will need to be collected and available:

- Investigator identification
- Patient identification code (eg, sex, age, or date of birth)
- Information on study drug (eg, start/stop date, dose and frequency of study drug administered)
- Description of event

In addition to the above information, the sponsor will require the investigator's assessment of the following:

- Severity of the SAE
- Relationship of the SAE to the study drug
- Outcome of the SAE

7.2.3 Follow-up Information of Serious Adverse Events

Appropriate diagnostic tests should be performed and therapeutic measures, as medically indicated, should be instituted. Appropriate consultation and follow-up evaluations should be carried out until the event has resolved or is otherwise explained by the investigator. For all SAEs, the investigator is obligated to pursue and provide information to the appropriate regulatory agencies. There should be routine follow-up through and including 30 days after the last administration of assigned study treatment or the investigator/patient decision to discontinue treatment, whichever occurs later, in all patients in order to monitor for the occurrence of SAEs. If an SAE continues after the 30-day evaluation period, then the patient must be followed until the event resolves or returns to baseline. The medical monitor may specify a longer period of time if required to assure the safety of the patient.

7.3 Other Safety Issues

7.3.1 Pregnancy

Females of childbearing potential and fertile males will be informed as to the potential risk of conception while participating in this study and will be advised that they must use effective contraception from randomization through at least 30 days after the end of treatment. A pregnancy test will be performed on each pre-menopausal female of childbearing potential immediately prior to randomization, and again at the End-of-Treatment Visit. A negative pregnancy test must be documented prior to administration of study drug. If a patient is confirmed pregnant during the trial, study drug administration must be discontinued immediately. The investigator must immediately notify the appropriate regulatory agencies of this event and record the pregnancy on a Pregnancy Form. The investigator must immediately report follow-up information to the appropriate regulatory agencies regarding the course of the pregnancy, including perinatal and neonatal outcome, regardless of whether the patient has discontinued participation in the study. If the pregnancy results in the birth of a child, additional follow-up information may be requested. If the pregnancy results in spontaneous abortion or stillbirth, the event should be reported as an SAE. Pregnancy outcomes must be collected for the female partners of any males who took study drug in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

7.3.2 Overdose

An overdose is defined as the accidental or intentional ingestion or infusing of any dose of a product that is considered BOTH excessive AND medically important. All occurrences of overdose must be reported as an SAE. Monitor adverse events as instructed in the schedule of events and as clinically indicated.

7.4 Unanticipated Problems

Unanticipated problems (UPs) are events (adverse events or not) that will be assessed by the PI as unexpected, related to study participation, **and** involving risk for participants or others. A reportable event that fulfills all of these characteristics is considered an unanticipated problem.
To be unanticipated, the event should be unexpected, not described in the study documents, or if described before, it is now presenting with increased severity, duration, or frequency.

To be related to study participation, the event should be probably or possibly related to study participation, due to drug, or as a consequence of a study procedure (even if the procedure is considered standard of care). If an event could be explained by the underlying medical condition, it is not considered related.

To involve risk for participants or others, the event may affect subjects' risk. Even if the event did not result in harm, if the subject could have been affected by the event (safety, rights, welfare), the event is reportable.

Unanticipated problems will be report to the IRB using the reportable events form within 10 calendar days from the date the PI first learn about the event if the problem was unanticipated, related and involving risk to participants or others or if happening at increase frequency, duration or intensity that previously anticipated.

8. Statistical Considerations

8.1 General Considerations

For the purposes of this protocol and all analyses, a month of treatment is defined as 28 days, and will be the same length as a cycle of treatment for both groups.

8.2 Analysis Population

Intention to treat (ITT) population: The ITT population includes all patients who are randomized to the study. Patients will be analyzed according to the treatment to which they were assigned.

Safety Population: The safety population includes all patients who have received at least 1 dose of EACA. Patients included in the safety population will be analyzed according to the treatment they received.

Per-protocol Population: The per-protocol population includes all patients who are randomized, receive at least one dose of study drug, and have no major protocol violations that could be expected to impact response data, such as: failure to satisfy one or more eligibility criteria, administration of other anti-cancer therapy concurrent with study drug, and administration of incorrect study drug doses. Major protocol violations will be finalized and documented prior to final data analysis.

8.3 Study Endpoints

8.3.1 Primary Endpoint

The primary objective of this study is to compare at the end of the study, the proportion of patients with major bleeding during the study period among patients randomized to receive either EACA or standard of care prophylactic platelet transfusions.

8.3.2 Secondary Endpoint

Secondary endpoints include:

- proportion of patients with any bleeding during the study period in each arm
- the total number of units of platelets transfused in each arm at the end of the study
- Quality of life as measured by in each arm before the study and at the end of the study
- Safety in each arm

8.4 Determination of Sample Size

This randomized, open-label phase II study is designed to compare proportion of patient with bleedings noted during the study. Patients will be assigned to receive prophylactic EACA (experimental arm) or prophylactic platelet (standard of care) in a 1:1 fashion. Previous studies suggest that the proportions of patients with major bleeding will be expected to be 8% and 30% in experimental arm and standard of care arm, respectively. With one sided Fisher's exact test, the sample size of 45 patients in each arm will achieve a power of 80% at the significance level of 5% to test whether prophylactic EACA can prevent major bleeding better than the standard of care. After adjusting for a 10% drop out rate, the actual required sample size will be 50 patients per arm. Therefore, the total sample size of the study will be 100 patients.

8.5 Efficacy Analysis

8.5.1 Definition of Efficacy Endpoints

The primary, key secondary and other secondary efficacy endpoints are listed in Section 3.2 and 3.3. This section defines the endpoints themselves and the associated conditions defining loss of those endpoints.

8.5.2 Primary Endpoint Analysis

The primary analysis of the primary endpoint will be performed using a one-sided fisher exact test to compare the proportions of patients with major bleeding during the whole study between the two arms. The significance level is set at 0.05. This primary analysis will be based on the ITT population.

8.5.3 Secondary Endpoint Analysis

One-sided t-test will be used to compare the total number of bleeding episodes noted during the study between the two arms. Two-sided t-test will be employed to compare the total number of units of platelets transfused at the end of the study between the two arms. Appropriate statistical tests (Chi-square test, t-test, Wilcoxon's rank sum test, etc.) will be conducted to compare the each score of the quality of life between the two arms before the study and at the end of the study, respectively. The change of each score of the quality of life from before the study to the end of the study will also be compared between the two arms. The safety in each arm will be also compared with Fisher's exact test. The analyses of secondary endpoints will be performed on the ITT population and the significance level will be kept at 0.05 for all tests.

For the primary and secondary efficacy endpoints, subgroup analyses will be performed by baseline potential prognostic factors. Subgroups will include: age, gender, race, underlying diagnosis, and other disease-related prognostic factors (disease status).

8.6 Safety Analysis

All patients receiving at least 1 dose of study drug will be considered evaluable for safety. Patients will be analyzed for safety according to the treatment which they received. Listings of laboratory test results will

also be generated, and descriptive statistics summarizing the changes in laboratory tests over time will be presented. Exposure to study drug over time will also be summarized. The AE incidence rates, as well as the frequency of occurrence of overall toxicity, categorized by toxicity grades (severity) will be described for each treatment arm and be compared between two arms using two-sided Chi-square test or t-test.

8.7 Quality of Life Analysis

Quality of life and health outcomes measures are being collected using the EQ-5D-5L instruments before the study and at the end of the study. Means and medians of raw scores of these questionnaires will be summarized for each treatment group for each domain and be compared between the two arms with t-test or Wilcoxon ranks sum test.

8.8 Interim Analysis

Three interim analyses are planned after 11 patients in each arm have been randomized and their results have been obtained. Each interim analysis will focus on the primary endpoint, the proportion of patients with major bleeding ever noted during the study. To maintain an overall Type I error rate of 0.05 (1-sided), an O'Brien Fleming approach will be used which requires a 1-sided p-value < 0.001 at the first interim analysis (at 25% of total sample size). If this boundary is not crossed, then the study will continue and the second interim analysis will be conducted at 50% of the total sample side which requires a 1-sided significance level of 0.004. If this boundary is not crossed at the second interim analysis then, the study will continue and a third interim analysis will be conducted at 75% of the total sample side which requires a 1-sided significance level of 0.019. If this boundary is not crossed, the final primary analysis will be performed after completing 100% of the sample size using a 0.043 one-sided significance level.

8.8.1 Impact on Conduct of Study

It is expected that the study will be fully enrolled prior to the conduct of the interim analysis. In the event that the study crosses the boundary at the interim analysis we would expect to continue patients on their randomized treatment arm to allow for continued assessment of other time points and the secondary endpoints.

8.9 Protocol Deviations and Violations

To be protocol-compliant, a patient must not have any major protocol deviations during the study period. Protocol deviations will be identified prior to final analysis and will be listed by treatment group in the clinical study report.

9.0 <u>Quality Control and Quality Assurance and Study Monitoring</u>

The investigator will be responsible for performing quality control and assurance checks. Before enrolling any patients into this study, the investigator will review the protocol, the CRFs and instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AEs with all personnel listed on the delegation of authority and FDA1572. The investigator will perform monthly evaluation of the conduct of the trial and perform the following:

- Review information recorded in the CRFs and verify against source documents
- Review data for safety information and to identify missing data
- Review protocol violations, out-of-range data, and other data inconsistencies

This study will be also be monitored by the DSMB Winship Committee that will address the following:

- Adherence to the protocol (the investigator should document and explain any deviation from the approved protocol)

- The completeness and accuracy of the CRFs and the dispensing and inventory record (adequate time and space for these visits should be allocated by the investigator)
- Compliance with regulations (the verification will require comparison of the source documents to the CRFs)

10. Ethical Conduct of the Study

This study will be conducted in accordance with the ethical standards that have their origin in the Declaration of Helsinki and that are consistent with GCP guidelines and the applicable regulatory requirements.

10.1 Institutional Review Boards Approval

The protocol and the informed consent document must have the initial and continuing review approval of the IRB. The signed IRB approval letter must identify the documents approved (ie, list the investigator's name, the protocol number and title, the date of the protocol and informed consent document, and the date of approval of the protocol and the informed consent document). Any advertisements used to recruit patients should also be reviewed by the IRB.

10.2 Patient Information and Consent

The study informed consent form will follow regulations that provide protection for human patients in clinical investigations and to describe the general requirements for informed consent. The informed consent document will contain all of the elements of the informed consent specified in the regulations. Nothing in this protocol or the regulations is intended to limit the authority of a physician to provide emergency medical care under applicable regulations. In addition, the investigator should be aware that some regulations require that he/she permit regulatory agencies to conduct inspections and review records pertaining to this clinical investigation.

10.3 Patient Confidentiality

Throughout the course of the study, all PHI record will be kept securely using password protected computer terminals. Access to the data will be on a need to know basis, therefore, only those investigators listed in the protocol will have access to the data. A high premium will be placed on ensuring that identifying information is not made available to staff engaged in routine care of the patient unless if necessary for the safe performance of their duties. For this reason, all research-related samples and clinical data will be de-identified using assigned study-specific registration numbers for such non-SOC procedures as much as possible.

The investigator agrees to keep all information in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC/REB. Study documents (investigators' brochures and other material) will be stored appropriately to ensure their confidentiality. The information provided to the investigator may not be disclosed to others without direct written authorization, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

10.4 Data Safety Monitoring Committee

Patient safety, study efficacy and compliance will be reviewed at the Hematology working group meeting. The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will also oversee the conduct of this study (every 6 months or annually – depending on the risk level of the protocol). This committee will review pertinent aspects of study conduct including patient safety, compliance with protocol, data collection and efficacy. The committee will review the charts of 10% of patients enrolled to the study and two of the first 5 patients entered to the study. The Committee reserves the right to conduct

additional audits if necessary. The Principal Investigator (PI) or designee is responsible for notifying the DSMC about the accrual of patients when the first 5 have been entered to the study. The PI or designee will also notify the DSMC of study status within 2 months before the next scheduled review is due.

11. Data Handling and Record Keeping

11.1 Case Report Forms and Study Records

Study-specific CRFs will be made available for the conduct of this study. Study data, contained in source documentation, will be entered into the CRFs for all patients enrolled in the study. All pertinent data records will be maintained on site for 5 years after completion or termination of the study.

11.2 Source Documents

The investigator agrees that regulatory agencies will have the right, both during and after this study, to conduct inspections and to audit and review medical records pertinent to the clinical study as permitted by the regulations. Patients will not be identified by name in any reports stemming from the study, and confidentiality of information in medical records will be preserved. The confidentiality of the patient will be maintained unless disclosure is required by regulations.

11.3 Retention of Data

Trial documents (including correspondence related to this clinical study, patient records, source documents, CRFs, study drug inventory records and IRB and sponsor correspondence pertaining to the study, original patient, laboratory, and study drug inventory records relating to the study) will be retained until 5 years after completion or termination of the study. Thereafter, records will not be destroyed but stored at an off-site location according to Emory policy.

11.4 Study Termination

The study will be terminated at any time for any of the following reasons:

- Failure to enroll patients
- Protocol violations
- Inaccurate or incomplete data
- Unsafe or unethical practices
- Questionable safety of the study drug
- Suspected lack of efficacy of the study drug
- Administrative decision

In the event of the termination of the Study, a written statement describing why the study was terminated prematurely will be made available by the investigator

12. References

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4. Heckman KD, Weiner GJ, Davis CS, Strauss RG, Jones MP, Burns CP. Randomized study of prophylactic platelet transfusion threshold during induction therapy for adult acute leukemia: 10,000/μL versus 20,000/μL. J Clin Oncol 1997;15:1143-1149
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7. Legler, T.J Frequency and causes of refractoriness in multiply transfused patients. Annals of Hematology 1997; 74: 185–189.
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9. European Medicines Agency. Antifibrinolytic medicine (aminocaproic acid), article 31. 2012.

Appendix 1

WHO grade	**Description**
0	No bleeding
1	Only petechial bleeding Including retinal bleeding without visual impairment
2	Mild blood loss Including melena, hematuria, hematemesis and hemoptysis
3	Gross blood loss Including any bleeding requiring red cell transfusion
4	Debilitating blood loss Including retinal and cerebral bleeding with high morbidity or fatal outcome