STATISTICAL ANALYSIS PLAN

Version 2.0
A Phase 1, Multi-Center, Open-Label, Dose Escalation Study of Thrombosomes in Bleeding Thrombocytopenic Patients in Three Cohorts

09 August 2019

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Cellphire Protocol 2017-1
Clinipace Study CEP17171

Prepared for Cellphire, Inc. (Sponsor)

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LIST OF ABBREVIATIONS

ABO	Blood types A, B, and O
AE	Adverse event
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical-Therapeutic-Chemical
BP	Blood pressure
BUN	Blood urea nitrogen
CBC	Complete blood count
CSP	Clinical study protocol
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
ETP	Endogenous thrombin potential
EKG	Electrocardiogram
GGT	Gamma glutamyl transferase
hs	High sensitivity
INR	International normalized ratio
LDH	Lactate dehydrogenase
MPV	Mean platelet volume
NCI	National Cancer Institute
PF	Prothrombin fragment
PI	Principal Investigator
PT	Preferred term or prothrombin time (context dependent)
RBC	Red blood cell
Rh	Rhesus
ROTEM	Rotational thromboelastometry
SAE	Serious adverse event
TAT	Thrombin antithrombin
TEAE	Treatment-emergent adverse event
TEG	Thromboelastography
TGA	Thrombin generation assay
TGPU	Thrombin generation potency units
WBC	White blood cell
WHO	World Health Organization

1 INTRODUCTION

This document outlines the methods of statistical analysis and data presentation associated with clinical study protocol (CSP) 2017-1, describing a Phase 1, multicenter, open-label, dose-escalation study. Within this study, the effects of escalating infusion doses of the investigational product, Thrombosomes®, will be assessed within a target population of actively-bleeding, thrombocytopenic patients (with platelet counts 5,000-70,000/µL). Patient inclusion will further be restricted to those with modified World Health Organization (WHO) bleeding severity scores of grade 1 (including only those patients with epistaxis, hematuria, oral petechiae, oropharyngeal bleeding, or bleeding at invasive or other wound sites) or grade 2, with bleeding due to hematologic/oncologic disease or bone marrow aplasia secondary to chemotherapy or radiotherapy. While the overall study design, study objectives and endpoints, and proposed methods for manipulating, analyzing, and presenting data are described below, the reader is referred to the CSP and case report forms for detailed descriptions of the investigational product, full list of patient inclusion/exclusion criteria, and data collection methods.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective of this study is to assess the effect of escalating infusion doses of Thrombosomes on the safety of actively-bleeding, thrombocytopenic patients.

Three dose levels, including 5 mL (9.45×10^7 particles/kg or 165 thrombin generation potency units [TGPU] per kg), 10 mL (1.89×10^8 particles/kg or 330 TGPU/kg), and 20 mL (3.78×10^8 particles/kg or 660 TGPU/kg), will be studied across 3 sequentially enrolled patient cohorts. Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (TESAEs), application of suspension or stopping rules, and abnormality or worsening in measures of bleeding severity, coagulation, hematology, serum chemistry, vital signs, and cardiac, physical, and neurologic statuses will be used as indicators of safety.

2.1.2 Secondary Objective

The secondary objective of this study is to assess potential efficacy of Thrombosomes for managing bleeding in actively-bleeding, thrombocytopenic patients.

Efficacy will be assessed within and across 3 sequentially enrolled patient cohorts, treated, respectively, at 3 escalating dose levels (see *Primary Objective* above). Post-infusion patterns showing stability or change toward clinical improvement in hematology measures will be used as preliminary indicators of possible product efficacy in bleeding management, and patterns in the receipt of transfused blood products will also be examined.

2.2 Study Endpoints

2.2.1 Primary Endpoints

Several primary endpoints will be quantified per patient cohort (i.e., by dose level), as well as overall (i.e., across all 3 dose levels):

- Overall frequency of (and number and percentage of patients who experience) TEAEs and TESAEs, including serious adverse drug reactions and treatment-related events specifically defining the study's suspension and stopping rules (i.e., thromboembolic events, acute lung injury, anaphylaxis, and death).
- Numbers and percentages of patients by highest WHO bleeding severity grade at baseline and post-baseline time-points, by highest severity grade at post-baseline time-points relative to baseline (allowing for assessment of shift), by both highest severity grade and bleeding site at baseline and post-baseline time-points, and by indication of a maximum severity grade ≥2 across bleeding sites at post-baseline time-points.
- Numbers and percentages of patients by grade-level change in WHO bleeding severity (e.g., -2, -1, 0, +1, +2, +3) from baseline to post-baseline time-points for the patient's most severe bleeding site at baseline, by indication of increased bleeding severity from baseline to post-baseline time-points for the patient's most severe bleeding site at baseline, and by indication of newly-developed bleeding sites from baseline to post-baseline time-points.
- Statistics describing (and/or graphics showing) central tendency and variability in coagulation, hematology, and serum chemistry measures across patients at baseline and post-baseline time-points, allowing for assessment of directional change in measures over time.
- Number and percentage of patients who shift from normal or clinically non-significant abnormal findings to clinically significant abnormal findings in coagulation, hematology, or serum chemistry measures between baseline and post-baseline time-points.
- Statistics describing central tendency and variability in vital signs, oxygen saturation (per pulse oximetry), and select 12-lead electrocardiogram (EKG) measures across patients at baseline and post-baseline time-points.
- Number and percentage of patients who shift in category of overall EKG interpretation from normal or clinically non-significant abnormal to clinically significant abnormal between baseline to post-baseline time-points.

2.2.2 Secondary Endpoints

Multiple secondary endpoints will be quantified per patient cohort (i.e., by dose level), as well as overall (i.e., across all 3 dose levels):

- Number and percentage of patients who, from baseline to post-baseline time-points, show either stability (i.e., no change) or an intermittent or sustained change toward clinical improvement in hematology measures, with or without reaching normal levels.
- Number and percentage of patients who receive transfused blood products following infusion.
- Statistics describing central tendency and variability in the numbers of units of blood products transfused following infusion.

3 STUDY DESIGN

3.1 Overall Design and Patient Participation

This study is a Phase 1, multicenter, open-label, dose-escalation study with a target study population of bleeding, thrombocytopenic patients. Patients from this population who show modified WHO grade-1 or grade-2 bleeding severity due to hematology/oncology diseases or bone marrow aplasia secondary to cancer chemo/radiotherapy will be enrolled and treated with the investigational product, Thrombosomes. Three cohorts of 8 patients each (for a total of 24 patients) will be sequentially enrolled, corresponding to 3 escalating infusion doses of Thrombosomes (5 mL [9.45×10^7 particles/kg or 165 TGPU/kg], 10 mL [1.89×10^8 particles/kg or 330 TGPU/kg], and 20 mL [3.78×10^8 particles/kg or 660 TGPU/kg]). The timing (or order) of patient enrollment, consequently, will dictate the dose level assignment of individual patients (see **Table 1**). Moreover, doses will be adjusted for patient weight.

Table 1 – Patient Cohort Assignment, Target Dose, and Safety Margins

Cohort	No. of Infusions	Target Mean Particles/kg	Target Mean TGPU/kg	Estimated Total Volume Infused[1]	Safety Margin[2]	
					Infused Particles/kg	Infused TGPU/kg
Cohort 1 (patients 1-8)	1	9.45×10^7	165	4.1 mL	300	301
Cohort 2 (patients 9-16)	1	1.89×10^8	330	8.2 mL	150	150
Cohort 3 (patients 17-24)	1	3.78×10^8	660	16.4 mL	75	75

Abbreviation: TGPU, thrombin generation potency units.

[1] Estimated Total Volume Infused is based on a 70-kg patient and mean Thrombosomes concentration (across lots) of 1.61×10^9 particles/mL with associated 2,800 TGPU/mL. Doses will be adjusted by patient weight in order to maintain the target Thrombosomes particle count per kg of patient body weight. Formula: Total Volume Infused in mL = ([patient weight in kg] x [desired dose in particles/kg or TGPU/kg, specific for the cohort]) ÷ Thrombosomes particles/mL or TGPU/mL provided with the specific lot of Thrombosomes. Example for Cohort 1: 4.1 mL = ([70 kg] x [9.45×10^7 particles/kg]) ÷ 1.61×10^9 particles/mL.

[2] Safety margins are based on the single acute toxicity study in New Zealand white rabbits (see CSP Section 1.7).

Written informed consent will be obtained from patients who are either actively bleeding or at risk of bleeding within 4 weeks following screening. Patients who are actively bleeding and determined through screening assessments to meet eligibility criteria for study participation will be immediately scheduled for infusion with Thrombosomes to occur within 4 days of screening. Patients who are not actively bleeding during screening but are at risk for bleeding within 4 weeks, based on medical history and projected clinical course, will be monitored for bleeding. If bleeding begins within 4 days (+6 hours), complete rescreening will not be necessary, but updated WHO bleeding assessment and complete blood count (CBC) tests will be required for determination of eligibility. If bleeding begins >4 days later but within 4 weeks of initiation of screening, rescreening (inclusive of all original screening assessments) will be necessary for

determination of eligibility. Given determination of eligibility through either scenario (i.e., completion of updated screening or rescreening assessments), the patient will be immediately scheduled for infusion with Thrombosomes to occur within 4 days. Patients who are not infused within 4 days of eligibility determination will (re-)enter rescreening, if no more than 4 weeks have passed since initiation of screening. Patients who are not infused within 4 weeks of initiation of screening will no longer be actively monitored for study eligibility or scheduled for infusion. However, they may subsequently re-enter the screening process at any time, if actively bleeding or determined to be at risk of bleeding. Patients will be classified as enrolled in the study at the onset of infusion.

Activities and assessments relating to the pre-infusion (screening) period, infusion (Day 1), and the post-infusion period (follow-up through Day 30 +2 days) will be performed as indicated in **Table 2** (see Section 3.3, Summary of Activities and Assessments). Importantly, stipulations exist concerning patient enrollment and the performance of assessments. For instance, patient infusions cannot occur on the same day. Once an eligible patient has been infused, the patient must reach Day 4 without a suspension or stopping rule event being reported before a subsequent patient may be infused (see Section 3.2, Safety Assessments). In addition, a 2-week interval of non-enrollment (i.e., no infusions), with all patients on study having completed the planned Day-6 follow-up visit (on Day 6 +4 days), must be met between cohorts to allow for an independent Data Monitoring Committee (DMC) to review all safety data from the previous cohort and provide recommendations on whether the study should advance to the next cohort (see **Appendix 1**).

The duration of each patient's participation in the study is expected to be approximately 4-8 weeks. Patients will be deemed "evaluable" after completing the planned Day-6 follow-up visit (on Day 6 +4 days) and considered to have completed the study after completing the planned Day-30 follow-up visit (on Day 30 +2 days). Time from first patient/first visit to last patient/last visit is expected to be 12 months. While the Investigators will make every effort to maintain patient participation through study completion, patients will be permitted to withdraw their consent for participation at any time, and circumstances may arise supporting the decision of the Investigator(s) to terminate the patient's participation, including:

- Non-compliance (e.g., no-show for scheduled visit, impairment due to drugs/alcohol, agitation/disruption during visit, inability to follow clinic rules concerning conduct)
- Safety issues (e.g., patient does not meet inclusion criteria for ongoing stages of the study, clinic safety due to unacceptable conduct, study cancelled due to product safety)
- Sponsor-initiated study termination
- Investigator-initiated study termination
- IRB of record or FDA study termination

3.2 Safety Assessments

The Primary Objective of this study is to assess patient safety across increasing infusion dose levels of Thrombosomes. This will be principally achieved by monitoring patterns in the incidence of AEs and, in particular, SAEs. An AE is any untoward or unfavorable medical occurrence in a study subject that does not necessarily have an underlying relationship with the investigational product. An AE can be any undesirable sign (e.g., an abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with use of the investigational product. As described in Section 2.2.1, Primary Endpoints, safety assessments supporting the identification of AEs will include:

- Coagulation measures.
- Hematology measures.
- Routine serum chemistry measures.
- Special serum chemistry measures (troponin).
- Vital signs, plus pulse oximetry readings.
- 12-lead EKG measures.
- Physical/neurologic status.

All AEs will be described by (a) timing of the event relative to infusion start (pre-treatment AE vs. treatment-emergent AE [TEAE]), (b) system organ class (SOC) and preferred term (PT) per version 20.0 of the Medical Dictionary for Regulatory Activities (MedDRA), (c) seriousness of the event (i.e., classification as SAE), (d) criteria satisfied for SAE classification, (e) severity of the event, (f) relationship with the underlying disease, and (g) relationship with the investigational product. While data will be reported for all AEs documented within the study (i.e., both non-serious and serious), data describing all AEs will be analyzed through the Day-6 visit, and data specifically describing SAEs will be analyzed through the Day-30 visit.

An SAE is an AE that may be significant enough to lead to changes in the way the investigational product is developed or administered (e.g., adjustment to dose levels, target population, monitoring schemes, and patient consent forms). Furthermore, an SAE may result in any of the following outcomes, which, in this study, represent criteria for AE categorization as "serious".

- Death
- Life-threatening situation (patient is at immediate risk of death)
- In-patient hospitalization (excluding those for study therapy or placement of an indwelling catheter, unless associated with other SAEs)
- Prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect in the offspring of a patient who received study drug
- Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or require medical or surgical intervention to prevent the outcomes listed above

Event severity will be graded on a scale of 1-5 per version 4.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), with grades defined as shown below. All events of grade 4 or 5 will be reported as SAEs.

- Grade 1 (mild): Does not interfere with routine activities; minimal level of discomfort
- Grade 2 (moderate): Interferes with routine activities; moderate level of discomfort
- Grade 3 (severe): Unable to perform routine activities; significant level of discomfort
- Grade 4 (life-threatening): Requires hospitalization or emergency room visit
- Grade 5 (fatal): Results in death

In this study, an AE will be considered potentially attributable (related) to the investigational product if a high degree of certainty exists that (1) Thrombosomes presents a plausible biologic mechanism of action for causing the AE, (2) a temporal association exists between timing of the Thrombosomes infusion and onset of the AE, and (3) the AE itself cannot be explained by known

characteristics or conditions of the patient (e.g., underlying disease, concurrent illness) or other factors (e.g., use of concomitant medications). Categories of relatedness will include:

- Not related: No relationship to investigational product; applies to events for which evidence exists of an alternate etiology.
- Unlikely: Likely unrelated to the investigational product; likely related to factors other than the investigational product but relationship cannot be ruled out with certainty.
- Possibly: A temporal association between the AE and the administration of investigational product cannot be ruled out, but there may also be alternative etiologies such as the patient's clinical status or use of other therapies.
- Probably: A high degree of certainty of the relationship between the event and investigational product exists; a reasonable temporal association is recognized and the event cannot be explained by known patient characteristics or other factors.
- Definite: An association exists between receipt of the investigational product and occurrence of the event; any association with other factors has been ruled out.

Suspension Rule: This study will be suspended if an SAE is reported by a Principal Investigator (PI) who believes that the event is possibly, probably, or definitely related to the use of Thrombosomes but does not meet the study's stopping criteria (described below). Following SAE reporting by the PI, the Sponsor will corroborate relatedness of the SAE to the study product and suspend the enrollment and infusion of patients until further evaluation of the SAE is completed. A DMC, along with the Medical Monitor and PI who treated the patient, will meet ad hoc to review characteristics and outcomes of the event. The DMC will formulate final conclusions regarding SAE causality and provide recommendations for whether the study should proceed without changes, proceed with changes, or not proceed at all.

Stopping Rule: The Sponsor will stop patient enrollment if a reported SAE satisfies all 3 of the following criteria: (1) reported as death, a thrombotic or embolic event, an acute lung injury, or anaphylaxis; (2) reported within 48 hours of infusion with Thrombosomes (except for anaphylaxis, requiring reporting within 4 hours of infusion); and (3) considered to be probably or definitely directly related to Thrombosomes. If the study is stopped, the study will resume only after a complete review of the data has been performed by the Medical Monitor, all PIs, and the DMC and a determination has been made of reasonable doubt that the event is related to the product. Note that thrombotic and embolic events, collectively, include myocardial infarction, pulmonary embolism, venous thromboembolism, stroke, and transient ischemic attack. The CSP Appendices C, D, E, and G provide definitions for these events, as well as acute lung injury and anaphylaxis.

3.3 Summary of Activities and Assessments

Table 2 – Schedule of Activities and Assessments, Modified from CSP 2017-1 Table 4

Evaluation	Initial Screen	Rescreen[1]	Day 1 (baseline)[2]	1-h post-infusion ±15 min	6-h post-infusion -1 or +2 h	Day 2 24-h post-infusion ±3 h	If hospitalized			Day 6 (+4 d)	Day 30 (+2 d) (via phone)
							Day 3	Day 4	Day 5		
Visit Number:	**1**	**1A**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Sign informed consent form	X										
Verbally reconfirm consent		X	X	X	X	X	X	X	X	X	X
Medical history and complete physical exam[4]	X										
WHO bleeding severity	X	X	X	X	X	X				X	
Abbreviated physical exam[5]		X	X	X	X	X				X	
Pregnancy test (female only)	X	X									
Concomitant medications[11]	X	X	X	X	X	X	X	X	X	X	
Record transfused blood products[6]	X	X	X	X	X	X	X	X	X	X	
Thrombosomes infusion			X								
Vital signs[12]	X	X	X	Prior to infusion, then every 15 ±5 min after start of infusion until 2 h. Continue every 1 h ±5 min until 4 h, then at 6 h and 24 h ±10 min post-infusion.						X	
Pulse oximetry			X	Monitor continuously during vital signs assessment; record at same time-points as vital signs.							
Monitor for AEs			X	Prior to infusion, then every 15 ±5 min after start of infusion until 2 h. Continue every 1 h ±5 min until 4 h, then at 6 h and 24 h ±10 min post-infusion. Continue daily monitoring until discharged or Day 6.			X	X	X	X	X[3]
12-lead EKG[9]	X		X[9]		X						
Hematology CBC[6,7]	X	X	X	X	X	X	Daily CBC, at minimum			X	
ABO group, Rh type	X										
Coagulation testing[8]	X	X	X	X	X	X					
Routine chemistry[13]			X		X	X					
Special chemistry[13]			X		X	X					
Draw archive sample[10]	X									X	

Abbreviations: ABO, blood types A, B, and O; AE, adverse event; ALT, alanine transaminase; aPTT, activated partial thromboplastin time; AST, aspartate transaminase; BUN, blood urea nitrogen; CBC, complete blood count; EKG, electrocardiogram; GGT, gamma glutamyl transferase; hs, high sensitivity; INR, international normalized ratio; LDH, lactate dehydrogenase; MPV, mean platelet volume; PF, prothrombin fragment; PT, prothrombin time; RBC, red blood cell; Rh, Rhesus; ROTEM, rotational thromboelastometry; SAE, serious adverse event; TAT, thrombin antithrombin; TEG, thromboelastography; TGA, thrombin generation assay; WBC, white blood cell; WHO, World Health Organization.

[1] Complete rescreening will be performed on patients who preliminarily met eligibility criteria but were not actively bleeding at the time of initial screening and then started bleeding within 4 weeks. Patients who continue/begin bleeding and fully meet eligibility criteria within 4 days (+6 hours) of initial screening will not need require rescreening, except for re-assessment of WHO bleeding and CBC.

[2] Baseline may occur within 24 hours following initial screening (or rescreening). The WHO bleeding severity, CBC, and coagulation assessments are required at baseline, not more than 2 hours prior to infusion. Red cell transfusion must be specifically related to treatment of bleeding within 24 hours of onset of bleeding.

[3] Chart review for SAEs will occur from Day 1 through Day 30 (+2 days). Phone calls with the patient will occur to confirm whether the patient experienced an SAE or required emergency medical care at an outside facility.

[4] Complete physical examinations will include measuring height and weight, documenting medical history, and performing a general medical/neurological examination. Medical history will include previous transfusions with red blood cells, plasma, and/or platelets.

[5] Abbreviated physical examinations will include general appearance, cardiovascular, respiratory, extremity, abdomen, and head and neck assessments.

[6] Blood products may include packed red blood cells, whole blood, apheresis platelets, pooled whole blood derived platelets, cryoprecipitate, and plasma. In the event of a blood product transfusion occurring after Thrombosomes infusion on Days 1-6, CBC results will be required from a blood sample collected within 8 hours prior to transfusion and within 1 hour (+30 min) following transfusion.

[7] Hematology CBC analytes will include WBC, RBC, hemoglobin, hematocrit, platelets, MPV, neutrophils, lymphocytes, monocytes, eosinophils, and basophils. Daily CBC will be required, but all CBC data for each patient during hospitalization through Day 6 will be collected.

[8] During screening, coagulation testing will include only PT/INR, aPTT, D-dimer, and fibrinogen. At and following baseline, testing will include PT/INR, aPTT, D-dimer, fibrinogen, TAT, PF 1+2, TEG or ROTEM, and TGA. For baseline testing, PT/INR, aPTT, D-dimer and fibrinogen will be collected no more than 8 hours prior to infusion.

[9] EKG measures include only heart rate and QT interval with Fridericia's correction. The EKG will be repeated if performed more than 4 days before infusion.

[10] For each of the time-points that require archive samples, 2 10-mL samples will be drawn (1 for plasma and 1 for serum).

[11] Medications may include but will not be limited to over-the-counter remedies, herbal preparations, vitamins, supplements and intravenous fluids.

[12] Vital signs will include heart rate, respiratory rate, systolic and diastolic blood pressure, and body temperature.

[13] Routine chemistry will include Na, K, Cl, CO_2, glucose, BUN, creatinine, albumin, total bilirubin, Ca, AST, alkaline phosphatase, ALT, GGT, LDH, total cholesterol, and total protein. Special chemistry will include hs Troponin I and hs Troponin T.

4 SAMPLE SIZE CONSIDERATIONS

The sample size for this Phase 1 study was not statistically derived. Rather, the target sample size of 8 evaluable patients per each of 3 escalating infusion dose levels was selected to minimize the number of patients exposed to the study treatment and associated assessments, while also ensuring access to a reasonable number of study subjects to support the study's primary and secondary objectives. Importantly, patients will be considered "evaluable" based on satisfaction of the criterion for inclusion in the most restrictive analysis population, requiring completion of the target post-infusion follow-up of 6 days (see Section 5.3, Evaluable Population). Target sample sizes for individual study sites contributing to each patient cohort will adhere to a ratio-based rule-of-thumb of 1:5, which defines an upper threshold for the relative difference (or degree of imbalance) between the smallest (or lowest enrolling) and largest (or highest enrolling) sites (Ruvuna 2004). In applying this rule, enrollment at the largest site(s) may not exceed 5 times the enrollment at the smallest site(s) within each of the 3 Thrombosomes dose levels.

5 ANALYSIS POPULATIONS

5.1 Screened Population

The Screened Population will include all patients who provide written informed consent for study participation. Patients who withdraw consent, who do not complete all screening (or rescreening) assessments, who are ultimately verified as ineligible (based on unsatisfied inclusion criteria or satisfied exclusion criteria), and/or who do not receive the Thrombosomes infusion (e.g., when awaiting the infusion in queue for 4 weeks past the start of screening) will be classified as screening failures. The Screened Population will be used in descriptive analysis of the numbers of patients screened and failing to enter the study, both overall and by primary reason for failure.

5.2 Safety Population

The Safety Population will include all patients who were infused with Thrombosomes, regardless of duration of subsequent study participation or adherence to planned follow-up assessments. As patients will be considered enrolled at the start of infusion, the Safety Population will also represent an "enrolled population". The population will be used in descriptive analysis of patient characteristics and disposition, as well as in all safety analyses supporting the Primary Objective and select efficacy analyses supporting the Secondary Objective.

5.3 Evaluable Population

The Evaluable Population will include all patients from the Safety Population who completed the planned Day-6 follow-up visit (on Day 6 +4 days) and, thus, were classified as "evaluable". The Evaluable Population will be used, along with the Safety Population, in select efficacy analyses supporting the Secondary Objective.

6 CONSIDERATIONS FOR DATA HANDLING AND ANALYSIS

6.1 Programming Environment

All data manipulation and statistical analyses will be performed using SAS statistical software (version 9.4 or later; SAS Institute Inc., Cary, NC).

6.2 Nominal Visits and Visit Windows

For each patient, infusion of Thrombosomes will occur on Day 1. Screening, baseline (pre-infusion), and post-infusion activities and assessments will correspond to specific nominal visits and time-points, as shown below in **Table 3**. Note that each nominal visit/time-point has an associated window, defined as the range in time (e.g., study days, hours, or minutes) during which the scheduled activities or assessments must be performed. Activities and assessments performed outside of these windows will be labeled "unscheduled". Data collected from unscheduled activities/assessments will be incorporated into patient-level data listings but will not necessarily be included in population-level data summaries (i.e., tables and/or figures) presented by visit/time-point. As appropriate (e.g., depending on sample size), data from unscheduled visits/time-points will be either entirely excluded from data summaries or compiled between scheduled visits/time-points for intermixed scheduled/unscheduled data presentation.

Table 3 – List of Nominal Visits and Time-Points

Nominal Visit/Time-Point	Scheduled Study Day	Day/Time Window
Screening[1]	Days -28 to Day -1	Any time during Days -28 to Day -1
Baseline	Day 1	Any time pre-infusion during Day 1[2]
Thrombosomes Infusion	Day 1	None; represents time-point 0 and provides reference for nominal visits and time-points
1-hour post-infusion	Day 1	±15 minutes
6-hour post-infusion	Day 1	-1 to +2 hours
24-hour post-infusion	Day 2	±3 hours
Day 3[3]	Day 3	Any time during Day 3
Day 4[2]	Day 4	Any time during Day 4
Day 5[2]	Day 5	Any time during Day 5
Day 6	Day 6	+4 days (any time during Days 6-10)
Day 30	Day 30	+2 days (any time during Days 30-32)

[1] If the patient is not actively bleeding at the time of screening but bleeding occurs within 4 days (+6 hours) of initial screening, the patient will not be rescreened (just WHO bleeding severity and CBC assessments will be repeated). If the patient is not actively bleeding at the time of screening but bleeding occurs >4 days and within 4 weeks of initial screening, the patient will be wholly rescreened and, following verification of eligibility, then enrolled and infused.

[2] Baseline assessments may occur any time preceding infusion on Day 1, except for the assessments of WHO bleeding severity, CBC, and coagulation. These assessments will be required to occur within the 2 hours preceding infusion.

[3] Relevant only if the patient is hospitalized.

6.3 Data Derivations based on Timing

For a given date within the screening period, the sequence number identifying the study day will be computed as the relevant screening date minus the date of Day 1 (i.e., screening date – date of Day 1). For a given date on/following infusion with Thrombosomes, the sequence number identifying the study day will be computed as the relevant infusion (or post-infusion) date minus

the date of Day 1 plus 1 day (i.e., infusion or post-infusion date – date of Day 1 + 1) to allow for inclusion of Day 1 within the computed period.

The following will define prior medication use versus concomitant medication use:

- Prior medication – any medication last used by a patient within the 4 weeks immediately preceding the date of Thrombosomes infusion. Anti-coagulant medications represent an exception, with the applicable range in dates ending at 48 hours before infusion.
- Concomitant medication – any medication taken on or after the date of Thrombosomes infusion through the Day-6 visit. Anti-coagulant medications represent an exception, defined as concomitant if taken at any time during the 48 hours preceding infusion through the Day-6 visit.

Baseline values for all assessment variables will be based on data collected during the latest assessment procedure performed prior to infusion with Thrombosomes. Unless otherwise specified, the change-from-baseline (CFB) value corresponding to any quantitative post-infusion assessment variable will be calculated by subtracting the baseline assessment value from the relevant post-infusion assessment value. If either the baseline or post-infusion assessment value is missing, then the CFB value will also be set to missing.

Pre-treatment AEs and treatment-emergent AEs (TEAEs) will adhere to straightforward definitions, with pre-treatment events occurring prior to start of the Thrombosomes infusion on Day 1 and treatment-emergent events occurring at or following the start of infusion.

6.4 Missing Values

For all patients enrolled and all activities and assessments performed, every effort will be made to achieve complete data collection. Imputation is not planned for missing data, other than for missing date/time values. The missing component(s) of incomplete dates (e.g. start or stop dates of TEAEs, concomitant medication use, events/conditions in medical history) will be assumed to be the most conservative value possible. For example, if the start date is missing the day value, then the first day of the month will be imputed for study day computations. If the end date is missing the day value, then the last day of the month will be imputed. A similar approach will be used for missing month and year components. For complete dates but missing start or end times, values marking the beginning of the day (00:00:00AM) or end of the day (23:59:59PM), respectively, will be imputed. Importantly, date/time imputation will be used for computational purposes only; actual data values (as they appear in the database) will be presented in all patient-level data listings. Patients who withdraw consent for study participation or are lost to follow-up will be included in data summaries and analyses to the point of last contact.

6.5 Strata and Covariates

No stratified analyses or covariate-adjusted analyses are planned for this study.

6.6 Subgroups

Three pairs of complementary subgroups of patients (for a total of 6 subgroups) will be defined based on receipt of therapy, including anticoagulant therapy, platelet transfusion, and transfusion of any blood product other than platelets, as follows:

- Subgroup 1: Patients who received anticoagulant therapy at any time between 48 hours before and 24 hours after Thrombosomes infusion.
- Subgroup 2: Patients who did not receive anticoagulant therapy between 48 hours before and 24 hours after Thrombosomes infusion.
- Subgroup 3: Patients who received platelets at any time between 6 hours before and 1 hour after Thrombosomes infusion.
- Subgroup 4: Patients who did not receive platelets between 6 hours before and 1 hour after Thrombosomes infusion.
- Subgroup 5: Patients who received any blood product other than platelets at any time between 1 hour before and 24 hours after Thrombosomes infusion.
- Subgroup 6: Patients who did not receive any blood product other than platelets between 1 hour before and 24 hours after Thrombosomes infusion.

Two additional complementary subgroups will be defined as shown below, based on the patient's living status on Day 30 but irrespective of completing the Day-30 visit:

- Subgroup 7: Patients who were alive on Day 30.
- Subgroup 8: Patients who died before Day 30.

Note that the survival outcomes of patients who are alive at last contact but withdraw study participation prior to Day 30 will be considered censored. These patients, consequently, will not be included in either Subgroup 7 or Subgroup 8.

6.7 Multiple Testing

No adjustments or corrections for multiple hypothesis testing are planned for this study.

6.8 Significance Level

Unless otherwise specified, all statistical analyses will be performed using two-sided hypothesis testing and a two-sided significance level (i.e., accepted type I error probability, α) of 0.05.

6.9 Descriptive Statistics and Notation

Unless stated otherwise, the term "descriptive statistics" refers to frequencies (counts and percentages) for categorical data and the number of patients (or samples), mean, median, standard deviation, interquartile range, minimum, and maximum for continuous data. When fewer statistics are needed for continuous variables and the appropriate (or desired) measure of centrality is the mean, the 95% confidence interval (CI) may be provided as the corresponding measure of dispersion. Likewise, when the appropriate (or desired) measure of centrality is the median, the corresponding dispersion measure to be provided may be the interquartile range or the combination of first and third quartiles, also referred to as 25th and 75th percentiles.

For the presentation of statistical results, standard approaches to determining significant digits will be used. Minimum and maximum values will be presented with the precision of the original values. Means, CIs, medians, interquartile ranges, and quartiles/percentiles will be rounded to 1 decimal place greater than (i.e., to the left of) the precision of the original value. Standard deviations will be rounded to 2 decimal places greater than the precision of the original value.

Percentages will be rounded to the nearest whole number, with values of "<1%" and ">99%" displayed for percentages approaching 0% and 100%, respectively. P-values will be presented with 3 decimal places of precision, and values less than 0.001 will be presented as "<0.001".

7 SUMMARY OF THE STUDY POPULATION

All summaries of the study population, as presented in tables or figures, will display descriptive statistics derived for each patient cohort (dose level) and all patients combined (see **Appendix 2** for proposed data summaries). Moreover, for most patient characteristics/outcomes described below, patient-level data listings will be provided to disclose detailed information.

7.1 Patient Screening, Enrollment, and Disposition

For patients in the Screened and Safety Populations, several summaries will be generated. In a single table, an overview of screening, enrollment, and disposition outcomes will be provided, including:

- Total number of screened patients.
- Numbers and percentages of screened patients representing screening failures by primary reasons for failed study entry, which will include:
  - Determination of inclusion criteria not met.
  - Determination of exclusion criteria met.
  - Determination of inclusion criteria not met and exclusion criteria met.
  - Patient withdrawal of consent for participation.
  - Patient lost to follow-up.
  - Other (e.g., continued non-bleeding status or delayed infusion due to stopped or suspended study status).
- Number and percentage of screened patients who were enrolled in the study.
- Numbers and percentages of enrolled patients who were classified as:
  - Evaluable (by completing the Day-6 visit).
  - Completed the study (by completing the Day-30 visit).
  - Discontinued the study (by discontinuing participation prior to the Day-30 visit) by reasons for discontinuation, which will include:
    - Adverse event.
    - Death.
    - Lost to follow-up.
    - Non-compliance by patient.
    - Physician decision.
    - Pregnancy.
    - Protocol deviation.
    - Site terminated by sponsor.
    - Study terminated by sponsor.
    - Withdrawal by patient.
    - Other.

In a second table, the numbers and percentages of patients included in each analysis population (Screened, Safety, and Evaluable), as well as each subgroup within the Safety Population, will be

presented. A patient flow chart will also be constructed to display the total numbers of patients screened, excluded from the study (representing screening failures), enrolled in the study, deemed "evaluable", and classified as either having completed or discontinued the study. Lastly, data describing enrollment and discontinuation statuses will be provided in separate patient-level data listings.

7.2 Deviations from the Clinical Study Protocol

Deviations will be described in a single table by the numbers and percentages of patients in the Safety Population who were associated with at least 1 deviation and with at least 1 major deviation. Protocol deviations deemed "major" are defined as those that may significantly affect the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety, or well-being. The numbers and percentages of patients falling into each deviation category (listed below) will be summarized for major and minor deviations combined.

- Inclusion/exclusion criteria
- Informed consent issue
- Out of window visit
- Protocol required evaluation not completed
- Non-compliance with study drug administration
- Received excluded treatment
- Developed withdrawal criteria but not withdrawn
- Other

Patient-level data listings will be used to disclose the timing, category, and major/minor status of all deviations and, separately, just the deviations specifically associated with non-adherence to inclusion/exclusion criteria.

7.3 Demographic and Other Baseline Patient Characteristics

Demographic and other baseline characteristics of patients recorded during screening will include age, sex, childbearing potential (if female), pregnancy status (if female), ethnicity (Hispanic or Latino, not Hispanic or Latino, not reported, and unknown), race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, and not reported), blood type (O, A, B, and AB), and Rh factor (positive, negative). For patients in the Safety Population, a single table will be generated to summarize all patient characteristics, with age summarized as a continuous variable and all others summarized as categorical variables. Additionally, a single patient-level data listing will be provided to disclose all individually recorded baseline characteristics, except pregnancy status. All pregnancy test results (including baseline and post-baseline results) will instead be disclosed in a separate patient-level data listing, dedicated to the results of chemistry laboratory tests.

7.4 Prior and Concomitant Medications

The use of prior medications and concomitant medications will be summarized in separate tables as the numbers and percentages of patients in the Safety Population who used medication within each reported hierarchy of WHO Drug Anatomical-Therapeutic-Chemical (ATC) Levels 1, 2, and 3 and WHO Drug preferred name. Medications with partial start and/or stop dates, which cannot be definitively categorized as prior or concomitant, will be considered concomitant. The details of prior and concomitant medication use will be disclosed in a single patient-level data listing.

7.5 Concomitant Procedures

In addition to concomitant medications (described immediately above), patients may undergo procedures during the study for reasons of an adverse event, their medical history, a concomitant treatment (including medication and another procedure), or other indication. In tabular form, concomitant procedures will be described by the number and percentage of patients in the Safety Population who received at least 1 concomitant procedure and by the numbers and percentages of concomitant procedure recipients who fell into each category of reason for procedure. Data describing concomitant procedures will also be provided in a patient-level data listing.

7.6 Medical and Surgical History

Medical/surgical history, including all clinically-significant events, conditions, and previous surgeries, will be described in a patient-level data listing encompassing all patients from the Safety Population.

7.7 Neurological Examination

A neurological examination, comprising 18 elements of assessment (listed below), will be performed at screening. In a single patient-level data listing, the categorical results of each assessment (normal, abnormal, and not done) will be disclosed for individual patients in the Safety Population.

1. With eyes closed: Romberg Test
2. With eyes opened: tandem gait
3. Walk on tip toes
4. Walk on heels
5. With eyes closed: check for pronator drift
6. Finger-to-nose test
7. With eyes opened: play the piano
8. Rapid tapping or alternating movements
9. With eyes closed: eyeballs shut tightly
10. With eyes opened: observe pupillary reflex
11. Grin
12. Stick tongue out
13. Rapid tongue movements
14. Visual fields by confrontation
15. Eye movements
16. Reflexes
17. Babinski
18. Fundoscopy

7.8 Laboratory Archive Samples

A single patient-level data listing will be provided to disclose the details of the laboratory archive samples collected during screening, including date/time of collection and reason if not collected.

8 SAFETY ANALYSES

Several measures of safety will be examined in this study, with all safety summaries and analyses based on data collected from the Safety Population. Statistics describing these measures will be presented within tables and figures and derived for each patient cohort (dose level), as well as all patients combined (see **Appendix 2** for proposed data summaries). For all measures, data will also be disclosed in patient-level data listings.

8.1 Adverse Events

For AEs in this study, tabular summaries will provide the total numbers of events (and numbers and percentages of patients who experience events) by such event characteristics as the timing of the event (pre-treatment AE vs. TEAE), timing of TEAE (through Day-6 visit vs. after Day-6 visit through Day-30 visit), MedDRA SOC x PT classification, seriousness of the event, criteria satisfied for SAE classification (including death), severity grade, relationship with the underlying disease, relationship with the investigational product, and subsequent discontinuation of study participation (see also Section 3.2, Safety Assessments, for definitions). Within SOC x PT summaries, each patient will be counted only once per SOC x PT combination. TEAEs indicated by abnormal coagulation results, TEAEs classified as neurological, and treatment-related TEAEs specifically defining the study's suspension and stopping rules (i.e., thromboembolic events, stroke, acute lung injury, anaphylaxis, and death) will also be summarized.

Tabular summaries will incorporate data describing all AEs (both non-serious and serious) reported through the Day-6 visit (potentially through Day 10) and only SAEs reported following the Day-6 visit and through the Day-30 visit (potentially through Day 32). To disclose the details of all AEs/SAEs falling into these time-frames, multiple patient-level data listings will be generated, dedicated to solely AEs, solely SAEs, SAEs deemed treatment-related, SAEs deemed at least possibly treatment-related, AEs leading to study discontinuation, patient deaths, and AEs classified as neurologic, thromboembolic, stroke, acute lung injury, and anaphylaxis. A separate patient-level data listing will be used to disclose any non-serious AEs that are documented after the Day-6 visit and, thus, not included in the tabular summaries.

8.2 WHO Bleeding Severity Scores

Within multiple tables, the numbers and percentages of patients will be presented by highest WHO bleeding severity score (no bleeding/grade 0, grade 1, grade 2, grade 3, or grade 4), with "highest severity score" defined as the score associated with the most severe bleeding site (given documentation of multiple sites) for the nominal time-point of interest. This distribution of highest WHO bleeding severity scores not only will be presented by nominal time-point but also will be presented by post-baseline time-points relative to baseline time-point (to allow for assessment of shift) and by both bleeding site and time-point. Differences between patient cohorts (dose levels) in the proportion of the study population showing grade 2 or higher bleeding severity for the most severe bleeding site will be tested for statistical significance per time-point using Fisher's exact test, with results displayed in a single table. To facilitate visual examination of trends, 1 or more of the summaries described above may be presented within supplementary clustered bar charts or line chart overlays.

The numbers and percentages of patients will also be presented by grade-level change in WHO bleeding severity (-2, -1, 0, +1, +2, and +3) from baseline to post-baseline time-points for the patient's most severe bleeding site at baseline, by indication of increased bleeding severity from baseline to post-baseline time-points for the patient's most severe bleeding site at baseline, and by

indication of development of new bleeding sites from baseline to post-baseline time-points. Lastly, the details of all WHO bleeding assessments will be presented in a patient-level data listing. To facilitate, within this listing, visual examination of possible post-infusion changes in bleeding severity or number of bleeding sites as associated with protocol-defined windows for the timing of infusion relative to screening (i.e., within 24 hours [as stipulated in CSP v1.1] vs. within 4 days [as stipulated in CSP v2.0+]), the data listing will be sorted first by the screening assessment dates of patients and then, within individual patients, by assessment date.

Importantly, patients with multiple bleeding sites may show tied bleeding severity scores. For summaries in which patients' highest severity scores will be reported independently by visit or by visit and bleeding site (as described in the first paragraph of this section), tied scores will have no consequence and the highest score reported will simply represent multiple bleeding sites. However, for summaries in which each patient's most severe bleeding site is selected at baseline and tracked across subsequent time-points (as described in the paragraph immediately above), bleeding site selection will depend on continued comparison of severity scores across subsequent time-points until the tie in severity score is broken. For example, if a tie in severity score exists at baseline, the bleeding sites involved in the tie will be compared using scores recorded at the patient's next visit (i.e., 1-hour post-infusion) and the site of highest severity will be selected. If scores are still tied at 1 hour following infusion, then scores from the 6-hour post-infusion visit will be compared, and so forth.

8.3 Clinical Laboratory Assessments

Laboratory assessments to be used in safety monitoring will include coagulation, hematology, and serum chemistry measures. For each assessment type, descriptive statistics summarizing the raw and CFB values of all measures (or select measures, see Hematology below) will be provided in 2 tables. As the Wilcoxon signed rank test will be used to test for difference between baseline and post-baseline values, the P-values derived during testing will be displayed within these tables, adjacent to corresponding CFB values. In 2 additional tables, the numbers and percentages of patients who show abnormal results and who show changes (shifts) from baseline in interpreted results (normal, abnormal non-clinically significant, and abnormal clinically significant) will be summarized per measure and visit. Measures corresponding to each assessment type will include those listed below, given sufficient data available for descriptive analysis (i.e., minimally 3 data points per computed statistic for each of 2 or more visits).

- Coagulation: PT, INR, aPTT, D-dimer, fibrinogen, TAT, PF 1+2, TEG (R time, K time, MA, angle), ROTEM (CT, CFT, angle, MCF), and TGA (lag time, time to peak, thrombin peak height, ETP)
- Hematology: WBC, RBC, hemoglobin, hematocrit, platelets, MPV, neutrophils, lymphocytes, monocytes, eosinophils, and basophils
  - Descriptive summaries of raw values will be presented in a single table for the select measures of WBC, RBC, hemoglobin, hematocrit, platelets, and MPV.
  - Descriptive summaries of CFB values and Wilcoxon signed rank test results will be presented in a single table for the select measures of WBC, neutrophils, lymphocytes, monocytes, eosinophils, and basophils.
- Chemistry: blood glucose, BUN, creatinine, sodium, potassium, chloride, calcium, CO_2, alkaline phosphatase, AST (SGOT), ALT (SGPT), total bilirubin, GGT, albumin, LDH, total cholesterol, total protein, and hs Troponin I (or hs Troponin T)

Results for select coagulation and hematology measures will also be provided in panels of spaghetti plots, with each panel corresponding to a single measure and incorporating 3 plots per row (1 plot for each patient cohort) and each plot presenting an overlay of the raw assessment results for individual patients through time. For each measure, 2 separate panels in total will be constructed. In the first panel (1 row x 3 columns and up to 1 page in length), individual patients will be represented without subgrouping. In the second panel (3 rows x 3 columns and up to 3 pages in length, given 1 row per page), line colors or patterns will be used to distinguish patients as belonging to Subgroup 1 or 2 (did or did not receive anticoagulant therapy; row 1), Subgroup 3 or 4 (did or did not receive platelet transfusion; row 2), and Subgroup 5 or 6 (did or did not receive any blood product transfusion other than platelets; row 3). Panels will be constructed for all measures listed below, given available data.

- Coagulation: INR, aPTT, D-dimer, fibrinogen, TAT, PF 1+2, TEG R time, TEG MA, TGA time to peak, and TGA thrombin peak height
- Hematology: WBC, hemoglobin, and platelets

Pertaining solely to the measure of WBC count, a single table will be produced to provide descriptive summary of the numbers and percentages of patients with abnormal results by visit and living status (Subgroup 7 vs. 8; see Section 6.6). Given the potential for lab normal ranges (and, thus, classification of WBC count results as abnormal) to differ across study sites, a second table will display the numbers and percentages of patients at different WBC count levels (defined using quantiles of raw WBC counts across all measurements, patients, and sites) by visit and living status. To facilitate visual examination of trend, this latter summary may also be presented within a supplementary clustered bar chart, line chart overlay, or panel of survival curves. Lastly, multiple data listings will be produced to disclose the details of sample collection and results for all clinical laboratory assessments performed per patient.

8.4 Vital Signs, Pulse-Oximetry, Height, Weight, and EKG Assessments

Using descriptive statistics, continuous data describing vital signs, oxygen saturation (through pulse oximetry), and 12-lead EKG results will be summarized by time-point within a single table. Vital signs will include heart rate, respiratory rate, systolic and diastolic blood pressure, and body temperature, whereas EKG measures will include heart rate and QT interval with Fridericia's correction. The details of all vital sign measurements, as well as patient body height and weight, will be disclosed in a single patient-level data listing. In addition to these data presentations, a separate table will be generated to summarize the numbers and percentages of patients who show shifts from baseline in overall interpretation of EKG results (normal, abnormal non-clinically significant, and abnormal clinically significant) by time-point, and a separate patient-level data listing will be dedicated to individual EKG results.

8.5 Physical Examinations

Multiple physical examinations will be performed during the period of screening through the Day-6 visit. Findings deemed clinically significant during screening will be recorded as medical history, whereas clinically-significant findings from all later exams will be captured as TEAEs. To disclose the details of all exam findings, regardless of clinical significance, a patient-level data listing will be provided.

8.6 Infused Thrombosomes

A tabular summary of statistics describing the Thrombosomes infusion doses received by patients will be provided. Specifically, the statistics will describe the following elements:

- Total Volume of Thrombosomes Infused (mL), computed as: ([patient body weight in kg] x [target dose in particles/kg, specific for dose cohort]) ÷ (Thrombosomes lot concentration in particles/mL)
- Interrupted Infusion (Yes/No)
- Reason for Interruption (Adverse Event, Infusion Site or Equipment not Functioning, Patient Declined Infusion, or Other)
- Total Number of Thrombosomes Particles Infused, computed as: (Thrombosomes lot concentration in particles/mL) x (Total Volume of Thrombosomes Infused in mL)
- Total Number of Particles Infused per Kilogram of Patient Body Weight (particles/kg), computed as: (Total Number of Thrombosomes Particles Infused) ÷ (patient body weight in kg)

A data listing will be provided to disclose the elements above for each patient. Note that standard units of calculation and presentation (i.e., particles vs. TGPU and particles/kg vs. TGPU/kg) will be selected prior to database lock. See also Section 3.1, **Table 1**, for more information.

8.7 Unscheduled Visits

A single patient-level data listing will be provided to disclose the details of all assessments performed during unscheduled visits, including assessments intended to correspond to nominal visits but incidentally performed out-of-window.

9 EFFICACY ANALYSES

All efficacy analyses will be performed using data collected from the Safety Population. For select hematology measures, however, analyses will be additionally performed using data from the Evaluable Population. Results will be presented in tables and figures and derived for individual patient cohorts (dose levels), as well as all patients combined (see **Appendix 2** for proposed data summaries). Data describing individual patients will be disclosed in data listings.

9.1 Clinical Laboratory Assessments

Laboratory assessments to be used in efficacy analyses will include select hematology measures (hemoglobin, hematocrit, and platelets). Within a single table for each of 2 populations (Safety and Evaluable), the numbers and percentages of patients will be presented by categorized patterns of post-infusion change, including clinical improvement, stability/no change, and clinical worsening, for each of 2 post-infusion timeframes (infusion through the 24-hour post-infusion visit and infusion through the Day-6 visit). For each patient, categorization will require consideration of all measurements recorded across all time-points within the timeframe. For each hematology measure, clinical improvement and worsening will be defined as shown below. The category of stability/no change will apply by default when, for an individual patient, neither improved nor worsened conditions have been observed following infusion. When both improved conditions and worsened conditions have been distinctly observed at different time-points, the patient will fall into the category of clinical improvement.

Clinical improvement will be defined by:

- Hemoglobin increase of 1 g/dL
- Hematocrit increase of 3%
- Platelet count increase of 5,000/μL

Clinical worsening will be defined by:

- Hemoglobin decrease of 1 g/dL
- Hematocrit decrease of 3%
- Platelet count decrease of 5,000/μL

9.2 Transfused Blood Products

The types and numbers of units of blood products transfused will be recorded from the onset of screening through Day 6. Within multiple tabular and graphic summaries of transfusions, the number of units transfused at any given assessment will be defined as the total number of units transfused after the previous assessment and before/during the given assessment. Baseline reporting will be limited to the blood products transfused during the 24 hours immediately preceding Thrombosomes infusion; it should then follow that all units reported before such time will be reported as occurring during screening. Lastly, the number of whole blood platelet derived units will be expressed as 1 unit, equivalent to a single platelet apheresis unit per the transfusing facility's standard.

In a single table, the numbers and percentages of patients who receive transfusions will be summarized by visit, reason for transfusion (active bleeding surgical, active bleeding non-surgical, low platelet count, chronic disease, marrow hypoplasia, coagulopathy, and other), and blood product type (packed red blood cells, whole blood, apheresis platelets, pooled whole blood derived platelets, cryoprecipitate, and plasma). In a second table, the number of blood product units transfused (treated as a continuous variable) will be summarized by blood product type and visit using descriptive statistics. For visual assessment of the number of platelet units transfused through time, a panel of spaghetti plots will be provided, with each plot representing a single patient cohort and displaying an overlay of the raw numbers of platelet units transfused through time for individual patients. Lastly, 2 clustered bar charts will be constructed to display the mean number of platelet transfusions received per patient within the first 24 hours following infusion and during Days 3-6, with the bars representing patient cohorts and the clusters of bars (cohorts) being defined by nominal visit within the time-frame of interest. Details describing all transfusions, as well as all products comprising the transfusions, will be presented in a patient-level data listing.

10 OTHER ANALYSES

10.1 Interim Analysis

No interim efficacy analysis is planned for this study.

10.2 End-of-Study Analysis

Data analyses, including production of the tables, figures, and listings presented below (**Appendix 2**), will be performed after the last patient has completed or discontinued the study and the clinical database has been cleaned, quality checked, and locked.

11 SUMMARY OF CHANGES FROM THE CLINICAL STUDY PROTOCOL

This Statistical Analysis Plan (SAP) amendment incorporates significant edits to the entirety of the original SAP text, with some deviations in meaning from the latest version of the CSP. In large part, the edits have been made in order to insert greater detail and provide clarification for important definitions and descriptions. The most significant edits/deviations in text include:

CSP v2.0		SAP v2.0	
Text Statement/Description	**Section, Page(s)**	**Text Statement/Description**	**Section, Page(s)**
Primary Objective: "Assess the safety of infusing increasing doses (approximately 5 ml, 10 ml, and 20 ml) of allogeneic Thrombosomes which are equivalent to approximately 9.45 x 107 particles/kg or 165 TGPU per kg,… respectively."	Section 1.8.1, Page 13	Rephrased with same general meaning but added detail (i.e., explicit listing of safety indicators).	Section 2.1.1, Page 6
Secondary Objectives: "Assess the effect, on WHO bleeding score, of increasing doses of allogeneic Thrombosomes" and "Assess the effect of increasing doses of allogeneic Thrombosomes on measures of coagulation".	Section 1.8.2, Page 13	Rephrased to more generally focus on assessment of the potential efficacy of Thrombosomes.	Section 2.1.2, Page 6
All Cohorts: Detailed description of screening and enrollment processes refers to "enrolled patient", without explicit definition.	Section 1.9.2.1, Page 14	Slightly reorganized and rephrased, with explicit definition of "enrolled patient" added: "Patients will be classified as enrolled in the study at the onset of infusion."	Section 3.1, Pages 8-9
Primary Safety Endpoints: "The occurrence and frequency of AEs, SAEs, and thromboembolic events as determined by clinical signs and symptoms, physical exam including neurological assessment, and laboratory studies."	Section 1.9.9, Page 18	Expanded significantly to encompass a detailed list of endpoints, relating to AEs, WHO bleeding severity (including new bleed sites), clinical lab measures, vital signs, oxygen saturation, and EKG measures.	Section 2.2.1, Page 7
Secondary Safety Endpoints: "Describe the effect of increasing doses of allogeneic Thrombosomes on bleeding including changes in WHO bleeding grade" and "Describe the effect of increasing doses of allogeneic Thrombosomes on coagulation measures".	Section 1.9.9, Page 18	Rephrased to explicitly define endpoints and focus on quantification of post-infusion patterns in hematology measures and receipt of transfused blood products.	Section 2.2.2, Page 7
Patient Numbers: "… Approximate number of patients enrolled: 30… Maximum Number of Patients Completed: 24…", without explicit definition of "enrolled" or "completed".	Section 1.10.1, Pages 18-19	Added text to the description of overall study design in order to explicitly define "enrolled" and "completed".	Section 3.1, Page 9
Sample Size Justification: "… there is no statistical basis for the selection of the sample size. The sample size, 8 patients per cohort, was selected to provide a reasonable balance in order to assess safety while minimizing the number of patients potentially at risk."	Section 1.13, Page 21	Rephrased with same general meaning but added detail and description of the employed rule-of-thumb for limiting the sample size at individual study sites.	Section 4, Page 14

12 REFERENCES

Ruvuna F. Unequal center sizes, sample size, and power in multicenter clinical trials. *Ther Innov Regul Sci* 2004;38(4):387-394.

13 APPENDICES

13.1 Appendix 1 – Data Monitoring Committee

An independent Data Monitoring Committee (DMC) is required for this study and will function as the primary data and safety advisory group (see also the Cellphire 2017-1 DMC Charter for more information). The DMC will periodically review study results, evaluate the treatments for adverse events and serious adverse events, and make recommendations to Cellphire, which has the responsibility to accept, reject, or to modify the DMC's recommendations. The primary purpose of the DMC is to oversee the safety of the trials and make recommendations regarding the continuation, modification or termination of the study based on the adverse effects of Thrombosomes.

The DMC will monitor study progress and any patient deaths, SAEs, severe AEs, study withdrawals, and adherence to/use of suspension rules and stopping rules. Information regarding other safety variables (e.g., AEs from laboratory results) will be also be reviewed. Specifically, study progress and safety data that will routinely be reviewed in the DMC meetings include:

- All SAEs, AEs, and use of suspension and stopping rule criteria (see Section 3.2)
- Number of patients screened
- Number of patients who resulted in a screen failure and reasons for failed entry into the study
- Number of patients enrolled
- Number of patients who withdrew from the study and reasons for withdrawal
- Number of patients evaluable (i.e., those participating through Day 6)
- Number of patients who completed study.

The DMC will make recommendations to Cellphire concerning the continuation of the study based on their periodic or ad hoc review of the data at the end of each meeting. All records of DMC recommendations made at the end of each meeting will be provided to Clinipace by Cellphire. The DMC may provide the following recommendations to Cellphire:

- Continue the study according to the protocol and any related amendments.
- Modify the study protocol. Modifications could include, but are not limited to, inclusion/exclusion criteria, frequency of visits or safety monitoring, alterations in study procedure(s), or changes in duration of observation and follow-up.
- Discontinue the study (with provisions for orderly discontinuation in accord with good medical practice).
- Other recommendations (e.g., inform the investigators and patients of a safety concern).

Meetings may be requested by the DMC Chairperson at intervals the Chairperson considers appropriate to the study data review. A minimum of 3 meetings are required during the study. There will be 1 kick-off meeting and 1 meeting for each of Cohorts 1 and 2. The DMC will time their meetings such that they will be able to evaluate follow-up patient data through Visit Day 6 for the last patient enrolled in the Cohort under review, and all available patient data (including cumulative data from the previous Cohorts) through Day 30.

Unscheduled meetings may be called, to review new information that may impact the studies, by the Chairperson, at the request of the Sponsor, or as indicated by the criteria triggering ad hoc reviews. These triggers may include but are not limited to unexpected adverse events, adverse reactions, serious adverse events, suspected adverse reactions, unexpected adverse events, fatal or life-threatening adverse events, or due to an imbalance in the number of adverse events between

arms, or adverse effects from animal or pre-clinical studies. Eight unscheduled meetings are expected in the study.

Safety data files will be prepared and distributed to the DMC members; tables and listings will be provided. The safety tables and listings that will be provided to the DMC will include:

- Enrollment Data
- Summary of AEs
- Summary of TEAEs by MedDRA System Organ Class, Preferred Term, and Severity
- Summary of At Least Possibly Treatment-Related TEAEs by MedDRA System Organ Class, Preferred Term, and Severity
- Summary of TESAEs by MedDRA System Organ Class, Preferred Term and Severity
- Listing of At Least Possibly Treatment-Related SAEs
- Listing of Select Coagulation Testing Data
- Listing of Select Hematology Data
- Listing of Select Chemistry Data

13.2 Appendix 2 – Proposed Table of Contents for Tables, Figures, and Listings in the Final Cellphire 2017-1 Clinical Study Protocol, Sections 14 and 16.2

SECTION 14 – SUMMARY TABLES AND FIGURES (84)

14.1 Summaries of the Study Population

Table 14.1.1	Summary of Screened Subjects – Screened Population
Table 14.1.2	Summary of Subject Enrollment and Disposition – Safety Population
Table 14.1.3	Summary of Analysis Populations and Subgroups – Safety Population
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