CLINICAL STUDY PROTOCOL

A Prospective, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Large Simple Trial Evaluating the Use of BE1116 (4-Factor Prothrombin Complex Concentrate [Kcentra® / Beriplex®]) to Improve Survival in Patients with Traumatic Injury and Acute Major Bleeding

Study Number:	BE1116_3006
Study Product:	BE1116 (Kcentra® / Beriplex®; 4-Factor Prothrombin Complex Concentrate [Human])
Development Phase:	Phase 3
Short Title:	Evaluation of BE1116 (4F-PCC) in patients with traumatic injury and acute major bleeding to improve survival
Sponsor:	CSL Behring LLC 1020 First Avenue King of Prussia PA 19406, USA
Protocol Version:	Amendment 2
EudraCT Number:	2021-005060-21
IND Number:	27983
Protocol Date:	06 February 2024
Compliance:	This study will be conducted in accordance with standards of Good Clinical Practice (as defined by the International Council for Harmonisation) and all applicable national and local regulations

LIST OF PERSONNEL AND ORGANIZATIONS RESPONSIBLE FOR CONDUCT OF THE STUDY

A list of personnel and organizations responsible for the conduct of the study will be supplied to study sites as part of the Investigator's Study File. This list will be updated by CSL Behring (or delegate) and provided to the study sites as needed.

Where the phrase site "investigator" is written in this protocol, the site "sub-investigator" who is on the delegation log and has appropriate training can also have the responsibility mentioned for the investigator, when in accordance with Applicable Law.

REVISION HISTORY

Date	Version	Summary of Changes
22 October 2021	Original	Not applicable
20 June 2022	Amendment 1 (Global)	See Summary of Changes document for a description of all changes since the Original version of the protocol, together with the rationale for changes. See the redline version of Global Amendment 1 for viewing of all tracked changes since the Original version.
06 February 2024	Amendment 2 (Global)	See Summary of Changes document for a description of all changes since Global Amendment 1, together with the rationale for changes. See the redline version of Global Amendment 2 for viewing of all tracked changes since Global Amendment 1.

Clinical Study Protocol Synopsis

Title	A Prospective, Multicenter, Randomized, Double-Blind, Placebo-Controlled Large Simple Trial Evaluating the Use of BE1116 (4-Factor Prothrombin Complex Concentrate [Kcentra® / Beriplex®]) to Improve Survival in Patients with Traumatic Injury and Acute Major Bleeding
Study Number	BE1116_3006
Sponsor	CSL Behring (CSL)
Development Phase	Phase 3
Study Product	BE1116 (Kcentra® / Beriplex®; 4-factor prothrombin complex concentrate [human])
Indication	Treatment of acute major bleeding associated with traumatic injury
Study Summary and Overview	This is a prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group, large simple trial to investigate the efficacy and safety of a single intravenous (IV) infusion of BE1116 in subjects who have traumatic injury, with confirmed or suspected acute major bleeding and / or predicted to receive a large volume blood product transfusion. Randomization will be in a 1:1 ratio (BE1116:placebo) and stratified by study site. Subjects will receive a single IV infusion of either BE1116 or placebo, in addition to the study site's standard resuscitation methods and protocol. The dose of BE1116 will be either 2000 IU or 3000 IU, based on the weight of the subject that is estimated or measured on arrival at the hospital: • Weight < 75 kg (< 165 lbs): 2000 IU • Weight ≥ 75 kg (≥ 165 lbs): 3000 IU The study consists of: (i) a Screening and Randomization (Enrollment) Period; (ii) a Treatment Period; and (iii) an In-hospital Follow-up Period. <u>Screening and Randomization (Enrollment) Period</u> Screening will begin once the subject has arrived at the hospital, and eligibility will be assessed. This study involves subjects who cannot be prospectively identified and who have life-threatening medical conditions necessitating emergent intervention. Because of the

subjects' conditions, the emergent need for intervention, and the limited treatment window during which the investigational product (IP) must be administered for potential efficacy, it is anticipated that obtaining prospective Informed Consent from subjects or their Legally Acceptable Representatives may not be possible. For these reasons, the study will be conducted under emergency research Applicable Law which allows subjects to be enrolled into qualifying research without obtaining prospective Informed Consent. However, attempts to collect prospective Informed Consent must be made, if feasible, in accordance with Applicable Laws, and if prospective Informed Consent can be obtained from a subject or their Legally Acceptable Representative prior to enrollment, such Informed Consent must be obtained. Study sites must reference their country-specific Study Consent Manual (where available) for additional requirements. Study sites must follow Applicable Laws in the conduct of the study and should consult their legal counsel and Institutional Review Board (IRB) or Independent Ethics Committee (IEC) for any advice or guidance with respect to any Applicable Laws and IRB or IEC requirements.

Once a subject meets all the eligibility criteria, the trauma team (or other applicable site staff) will select and open the IP study kit (for IP reconstitution and administration) with the next available sequential subject number, and the subject will be considered randomized (enrolled). The date and time of opening the IP study kit (randomization) will be recorded.

Treatment Period

The start of the IP infusion must be within 90 minutes after arrival at the hospital.

Blinded, sealed IP study kits containing either BE1116 or placebo will be maintained in the trauma bay, or a location where they are readily accessible, at the study site at all times during the study.

In-hospital Follow-up Period

If Informed Consent is not obtained from a subject or their Legally Acceptable Representative prior to randomization, Informed Consent for continued participation will be sought after randomization in accordance with the country-specific Study Consent Manual (where available) and where required by Applicable Laws. Similarly, if during the study a subject regains capacity after they are enrolled, Informed Consent for continued participation from the subject shall be sought pursuant to the country-specific Study Consent Manual (where available) and where required by Applicable Laws. Study sites must reference

	their country-specific Study Consent Manual (where available) for additional requirements. Study sites must follow Applicable Laws in the conduct of the study. During the primary hospitalization, efficacy and safety data will be collected up to the time of death / hospital discharge / Day 30, whichever occurs first. If subject is discharged alive prior to 6 hours, then the subject will be followed up to assess 6-hour survival status, serious adverse events (SAEs), and adverse events of special interest (AESIs). Primary hospitalization is defined as the initial hospitalization following the trauma. An Independent Data Monitoring Committee (IDMC) will review results periodically during the study.
Primary Objective	The primary objective is to assess the efficacy of a single IV infusion of BE1116 on all-cause mortality within 6 hours after randomization in subjects who have traumatic injury, with confirmed or suspected acute major bleeding and / or predicted to receive a large volume blood product transfusion.
Primary Endpoint	The primary endpoint is all-cause mortality within 6 hours after randomization.
Secondary Objectives	1. To assess all-cause in-hospital mortality up to 24 hours after randomization 2. To assess all-cause in-hospital mortality up to 30 days after randomization 3. To assess the requirement for surgical or interventional radiological procedures to stop bleeding related to the primary injury up to 24 hours after randomization 4. To assess the safety of BE1116

Secondary Endpoints	1. All-cause in-hospital* mortality up to 24 hours after randomization 2. All-cause in-hospital* mortality up to 30 days after randomization 3. Surgical or interventional radiological procedures to stop bleeding related to the primary injury up to 24 hours after randomization 4. SAEs considered related to IP; and AESIs: • Thromboembolic events (TEEs), symptomatic or asymptomatic, and arterial or venous (eg, deep vein thrombosis, pulmonary embolism, ischemic stroke [including thromboembolic stroke], myocardial infarction) • Acute respiratory distress syndrome (ARDS) • Multiple organ failure • Acute kidney injury (AKI) requiring renal replacement therapy (dialysis, hemofiltration, or hemodiafiltration) **Note**: superficial thromboses will not be included as AESIs *In-hospital mortality will only be recorded and assessed for the primary hospitalization.
Study Duration	The study duration for an individual subject who dies while on the study is up to the time of death. For other subjects, the study duration is at least 6 hours and ends with hospital discharge, or 30 days, whichever comes first. If the subject is discharged alive prior to 6 hours, then the subject will be followed up to assess 6-hour survival status, SAEs, and AESIs. The overall study duration (ie, from screening of first subject through the end of the last subject's In-hospital Follow-up Period) will be approximately 3 years.
Number of Subjects	It is planned to enroll up to 8000 subjects (4000 per treatment arm).

Study Population and Criteria for Eligibility	Inclusion criteria 1.A2. (a) Estimated or actual age ≥ 15 years. Older minimum age is required in some locations. *FOR United Kingdom*: Estimated or actual age ≥ 16 years *FOR Australia*: Estimated or actual age ≥ 18 years **AND** (b) Estimated or actual weight ≥ 50 kg (110 lbs) 2.A1. Traumatic injury with: (a) confirmed or suspected acute major bleeding; and / or (b) Revised Assessment of Bleeding and Transfusion (RABT) score ≥ 2 3.A1. Not applicable. Criterion 3 was deleted at Global Amendment 1 4. Activation of massive transfusion protocol 5.A2. Initiation of blood product transfusion (Whole Blood or Red Blood Cells or Platelets or Plasma has started to enter the patient's body) 6.A1. Anticipated start of IP infusion within 90 minutes after arrival at the hospital Exclusion criteria 1.A2. Healthcare professional cardiopulmonary resuscitation including chest compressions for ≥ 5 consecutive minutes at any time before randomization 2. Isolated penetrating or blunt cranial injury, or exposed brain matter 3. Known anticoagulation treatment or a history of a TEE, within the past 3 months 4.A1. Isolated burns estimated to be > 20% total body surface area or suspected inhalational injury 5. Ground level fall 6. Drowning or hanging 7. Subject transferred from another hospital 8. Known heparin-induced thrombocytopenia 9. Known hereditary disorders that significantly increase prothrombotic risk such as hereditary antithrombin III deficiency, Factor V Leiden, etc. 10. Known or suspected pregnancy 11. Known anaphylactic or severe systemic reactions to BE1116 or any components in BE1116 including heparin, Factors II, VII, IX, X, Proteins C and S, antithrombin III, and human albumin

	12.A2. Known prisoner at time of enrollment 13. Known "Do Not Resuscitate" order 14.A2. (a) *FOR all study sites*: Subject or Legally Acceptable Representative voiced an objection to participation in the trial **OR** (b) *FOR United States*: A family member voiced an objection to participation in the trial or subject was wearing an "opt-out" bracelet. 15.A1. Known participation in another interventional clinical study except with prior documented agreement from the sponsors 16.A1. Known treatment with any prohibited medications including 3F-PCC, 4F-PCC, aPCC (FEIBA), and / or Factor VIIa after trauma and prior to randomization 17.A2. Normal level of consciousness (Glasgow Coma Scale score of 15). 18.A2. Moribund patient with devastating injuries expected to die within 1 hour of hospital arrival.
Study Product Dose, Dosing Regimen and Administration	BE1116 (4-factor prothrombin complex concentrate [4F-PCC] containing human coagulation Factors II, VII, IX, and X, Protein C, and Protein S), powder for reconstitution with sterile water for injection A single dose will be administered by IV infusion. The dose is dependent on body weight (estimated or measured): • Weight < 75 kg (< 165 lbs): 2000 IU • Weight ≥ 75 kg (≥ 165 lbs): 3000 IU
Comparator Product, Dose, Dosing Regimen and Administration	Placebo to match BE1116

Efficacy Assessments	Efficacy data will be recorded from medical records. The survival status of the subject during primary hospitalization will be recorded from randomization up to the time of death, hospital discharge, or Day 30, whichever occurs first. The survival status check during primary hospitalization will be at 24 hours. If subject is discharged alive prior to 6 hours, then the subject will be followed up to assess 6-hour survival status, SAEs, and AESIs. Surgical or interventional radiological procedures performed to stop bleeding related to the primary injury, through the first 24 hours after randomization, will be recorded. Transfusion of blood products and IV fluids administered before arrival at the hospital through the first 24 hours after randomization will be recorded.
Safety Assessments	SAEs and AESIs will be recorded from the time of randomization through the end of the In-hospital Follow-up Period in each subject (ie, up to the time of death / hospital discharge / Day 30, whichever occurs first; if subject is discharged alive prior to 6 hours, then the subject will be followed up to assess 6-hour survival status, SAEs, and AESIs). Pregnancy status will be recorded from medical records (if available); pregnancies in female subjects will also be recorded. Daily assessments of ARDS, multiple organ failure, and AKI requiring renal replacement therapy will be recorded when a subject is in the intensive care unit (ICU). ICU assessments will be collected from the medical record of the subject using data collected as part of standard of care.
Other Assessments	To assess medical resource utilization, start and stop dates and times of ventilator use, time in the ICU, and primary hospitalization will be recorded.
Statistical Analyses	The Intent-to-treat (ITT) Population will include all randomized subjects. The Modified ITT (mITT) Population will include all subjects who receive a complete or partial dose of BE1116 or placebo. In these populations, analyses will be based on the treatment to which subjects were randomized, regardless of which treatment they actually received. The Per-protocol (PP) Population will include all subjects in the ITT Population with no major protocol deviations that would potentially affect the assessment of the primary endpoint.

The Safety Population will include all subjects in the ITT Population who receive a complete or partial dose of BE1116 or placebo, based on the treatment actually received.

Primary efficacy endpoint

A Bayesian logistic regression will be used to compare all-cause mortality rate during the first 6 hours after randomization between the BE1116 and placebo arms, in the ITT Population.

Null Hypothesis: The all-cause 6-hour mortality rate in BE1116 is no better than control.

Alternative Hypothesis: The all-cause 6-hour mortality rate in BE1116 is lower than control.

Interim analyses will occur when 1/4 (2000), 1/2 (4000), and 3/4 (6000) of the targeted 8000 subjects have data for the primary outcome. A group sequential approach will be utilized. The study may be stopped if futility (nonbinding) criteria are met at any of the three planned interim analyses, or if efficacy criteria are met at Interim Analysis 2 or 3. The success threshold for each applicable interim analysis and final analysis will be calibrated to protect overall type I error at 2.5% depending on the actual number of subjects with data on the primary outcome.

The study will continue to enroll 8000 subjects unless it is stopped for success or futility at one of the interim analyses.

The following subgroups will be analyzed as subgroup analysis and sensitivity analysis for the primary endpoint: mechanism of trauma injury (any penetrating versus blunt), sex (male versus female), age (< 18 years versus 18 to 25 years versus 26 to 64 years versus > 64 years), weight-based dosing (2000 IU versus 3000 IU), and cause of death (hemorrhage versus non-hemorrhage). Additional subgroup and sensitivity analyses may be defined in the statistical analysis plan.

Secondary efficacy endpoints

After the primary endpoint is deemed successful, the efficacy-related secondary endpoints will be analyzed sequentially. A gated testing approach will be used to account for multiplicity, and testing will proceed in a stepwise manner conditioned on observing a statistically significant result at each endpoint.

All secondary efficacy endpoints will be analyzed using the ITT, mITT, and PP Populations. All-cause in-hospital mortality up to hospital discharge or 24 hours after randomization (whichever occurs first), and all-cause in-hospital mortality up to hospital discharge or 30 days after randomization (whichever occurs first),

	will be analyzed and summarized in the same manner as for the primary endpoint. The difference in proportion of subjects who undergo surgical or interventional radiological procedures to stop bleeding related to the primary injury up to 24 hours after randomization will be analyzed and summarized in a manner similar to the primary endpoint. Secondary efficacy endpoints will also be analyzed using the same subgroups listed above. <u>Safety endpoints</u> The safety endpoints will be assessed using the Safety Population, unless otherwise noted. The number and proportion of subjects with SAEs considered related to IP that occurred during primary hospitalization within the 30 days after randomization will be summarized by treatment arm. In-hospital TEEs and AESIs will also be summarized by treatment arm.

Schedule of Assessments

Study Period	**Screening[A] and Randomization (Enrollment) Period**	**Treatment Period [B]**	**In-hospital Follow-up Period**	
Study Day	**1**		**Up to Death / Hospital Discharge / Day 30 [C]**	
Time Point	**0 to 90 minutes after hospital arrival**		**0 to 24 hours post-randomization**	**Up to 30 days post-randomization**
Informed Consent [D]	X			
Informed Consent for Continued Participation [D]		X	X	X
Vital Signs, Body Weight, Height [E]	X			
Glasgow Coma Scale [F]	X			
RABT Score [G]	X			
Inclusion and Exclusion Criteria [H]	X			
IP Study Kit Opened (Randomized [Enrolled]) [I]	X			
Hematology, Coagulation, and Arterial or Venous Blood Gas [J]	X			
Start of IP Infusion [K]		X		
IP Accountability [L]		X	X	
SAEs and AESIs [M]	X	X	X	X
Recordings From Medical Records (as applicable):				
Demographics [N]	X			
Medical History, Charlson Comorbidity Index [O]	X			
Prior / Concomitant Medications [P]	X	X	X	X
Concomitant Procedures [Q]	X	X	X	X
Survival Status - Date and Time of Death [R]	X		X	X

Study Period	**Screening[A] and Randomization (Enrollment) Period**	**Treatment Period [B]**	**In-hospital Follow-up Period**	
Study Day	**1**		**Up to Death / Hospital Discharge / Day 30 [C]**	
Time Point	**0 to 90 minutes after hospital arrival**		**0 to 24 hours post-randomization**	**Up to 30 days post-randomization**
Blood Product Transfusions, IV Fluids [S]	X	X	X	
Surgical and Interventional Radiological Procedures Through First 24 Hours After Randomization [T]	X	X	X	
Mode of Transport [U]	X			
Life-saving Interventions [V]	X	X	X	
Mechanism of Injury [W]	X			
Date and Time of Call to Emergency Services and Arrival at Trauma Scene [X]	X			
Hospital Arrival Time and Hospital Admission Time [Y]	X			
Injury Severity Score [Z]	X			
Pregnancy Status [ZA]	X			
ICU Assessments [ZB]			X	X
Medical Resource Utilization [ZC]	X			
Discharge / Transfer Location [ZD]	X			

AESI = adverse event of special interest; AKI = acute kidney injury; ARDS = acute respiratory distress syndrome; eCRF = electronic case report form; ICU = intensive care unit; IEC = Independent Ethics Committee; IP = investigational product; IRB = Institutional Review Board; IRT = interactive response technology; IV = intravenous; min = minute(s); RABT = Revised Assessment of Bleeding and Transfusion; SAE = serious adverse event.

A Screening assessments must be performed prior to randomization but may be recorded in the eCRF after randomization.

B Treatment period is defined as the start of IP infusion through the completion of IP infusion.

C Subjects will be followed up until death, discharge from hospital, or Day 30, whichever occurs first. Transfer to another healthcare facility will be considered as discharge from hospital. If subject is discharged alive prior to 6 hours, then the subject will be followed up to assess 6-hour survival status, SAEs, and AESIs.

D Informed Consent according to Applicable Laws. Study sites must reference their country-specific Study Consent Manual (where available). Study sites must follow Applicable Laws in the conduct of the study. For the avoidance of doubt, this definition of Informed Consent includes assent of a minor subject along with corresponding Informed Consent of their Legally Acceptable Representative, when allowed by Applicable Law. Informed Consent, Applicable Law, and Legally Acceptable Representative are as defined in Appendix 8.

E Vital signs obtained as part of standard of care will be recorded at Screening prior to infusion, except as described. These include supine systolic and diastolic blood pressure (mmHg), pulse rate (bpm), respiratory rate (breaths per min), pulse oximetry (%), and body temperature (°C). Body weight (kg) will be estimated or measured on arrival at the hospital and used to define the dose of IP. If estimated, weight may also be subsequently measured. Height (cm) will be measured or taken from medical history.

F Glasgow Coma Scale to be assessed at Screening and record individual components if available, otherwise total score; see Appendix 3.

G If applicable. RABT score ≥ 2 may be used to fulfill inclusion criterion assessment.

H All eligibility criteria should be met, including initiation of blood product transfusion (Whole Blood or Red Blood Cells or Platelets or Plasma has started to enter the patient's body).

I Time zero (0 hours) = IP study kit opened (randomization) after eligibility has been checked.

J To be recorded from medical records (if available). The initial hematology, coagulation, and blood gas measurements only will be recorded in the eCRF from medical records. Initial = the first value obtained after arrival at the hospital prior to IP infusion. Hematology includes hemoglobin, hematocrit, and platelets; coagulation includes international normalized ratio and / or prothrombin time; and arterial or venous blood gas (if reported by clinical laboratory: base excess; if base excess not reported by clinical laboratory, then the study site will collect the following parameters so that base excess can be calculated: pH, pCO_2, pO_2, and HCO_3).

K The start of the IP infusion needs to occur within 90 minutes after arrival at the hospital.

L IP accountability will be performed in the IRT system when feasible within 24 hours after randomization.

M All SAEs and AESIs will be recorded, reviewed, and assessed for relatedness. The observation period for the reporting of SAEs and AESIs for an individual subject will start at the time of randomization and finish with the end of the In-hospital Follow-up Period (ie, up to the time of death / hospital discharge / Day 30, whichever occurs first; if subject is discharged alive prior to 6 hours, then the subject will be followed up to assess 6-hour survival status, SAEs, and AESIs).

N Demographics will be recorded when feasible. Demographic data include sex, race, ethnicity, and other factors according to the eCRF and regulatory and local requirements. Either actual age or estimated age will be collected during Screening. The actual age of subjects will be recorded, once confirmed. An enrolled subject whose confirmed age does not meet the inclusion criteria must be reported to Sponsor and the IRB / IEC as a prompt reporting event.

O Medical history and the Charlson Comorbidity Index (see Appendix 6) will be recorded in the eCRF when feasible. Medical history should include all bleeding and coagulation history and surgical conditions, and any other pertinent findings.

P Medications that impact bleeding and coagulation (including antiplatelets) for at least 1 week prior to randomization will be recorded when feasible. Tranexamic acid (if administered) should be recorded. Prohibited concomitant medications administered from trauma time through 6 hours after randomization should be recorded. Any anticoagulants, thrombolytic agents, and procoagulants used to treat AESIs at any time through the study will be

recorded. In-hospital low-dose prophylactic anticoagulants are not considered concomitant medications.

Q Any surgical or interventional radiological procedures, or other life-saving interventions, used to treat an SAE or AESI at any time through the study will be recorded as a concomitant procedure.

R The survival status of the subject during primary hospitalization will be recorded from randomization up to the time of death, hospital discharge, or Day 30, whichever occurs first. The date and time of death / hospital discharge / Day 30 will be recorded, as applicable. The survival status check during primary hospitalization will be at 24 hours (the date and time of death / hospital discharge will be recorded, as applicable). If subject is discharged alive prior to 6 hours, then the subject will be followed up to assess 6-hour survival status, SAEs, and AESIs. The primary cause of death, as determined by the investigator, will be recorded.

S Transfusion of blood products before arrival at the hospital through the first 24 hours after randomization will be recorded according to the period in which the blood component transfusion started: before arrival at the hospital; from arrival at the hospital to the time of randomization; from randomization to 6 hours after randomization; and from 6 to 24 hours after randomization. Administration of IV fluids will also be recorded for the same time periods.

T All surgical or interventional radiological procedures performed to stop bleeding related to the primary injury, through the first 24 hours after randomization, will be recorded.

U Mode of transport to the hospital will be recorded.

V Prehospital life-saving interventions and any life-saving interventions performed on arrival at the hospital, will be recorded.

W Mechanism of injury (blunt, penetrating, or both) will be recorded.

X If applicable and available.

Y Hospital arrival time and hospital admission time may be the same time, but should be recorded per study site processes. Hospital arrival time will determine timing of IP administration.

Z The Injury Severity Score will be calculated and recorded (Appendix 4). The Injury Severity Score may be calculated after study completion.

ZA To be recorded from medical records (if available). Pregnancies in female subjects will be recorded.

ZB Daily assessments for ARDS, multiple organ failure, and AKI requiring renal replacement therapy will be recorded when a subject is in the ICU. ICU assessments will be collected from the medical record of the subject using data collected as part of standard of care.

ZC Medical resource utilization: start and end dates and times of ventilator use, days in ICU, and days in hospital during primary hospitalization will be recorded.

ZD Discharge / transfer information will be recorded (eg, transferred to another hospital, transferred to skilled nursing facility, transferred to in-patient rehabilitation, discharged to home, or transitioned to comfort care / palliative care). If subject is discharged within 2 days of enrollment, discharge time will also be recorded. Additionally, if the subject is designated “do not resuscitate”, the date and time (where applicable) will be recorded.

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List of Abbreviations

Abbreviation	Term
3F-PCC	3-Factor prothrombin complex concentrate
4F-PCC	4-Factor prothrombin complex concentrate
AE	Adverse event
AESI	Adverse event of special interest
AIS	Abbreviated Injury Scale
AKI	Acute kidney injury
ARDS	Acute respiratory distress syndrome
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CSL	CSL Behring
EC	Executive Committee
eCRF	Electronic case report form
EFIC	Exception From Informed Consent
FDA	Food and Drug Administration
FEIBA	Factor VIII inhibitor bypassing activity
FII, FVII, FIX, FX	Factor II, VII, IX, X
FFP	Fresh frozen plasma
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator's brochure
ICE	Intercurrent event
ICH	International Council for Harmonisation
ICU	Intensive care unit
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IP	Investigational product
IRB	Institutional Review Board
IRT	Interactive response technology
ISS	Injury Severity Score
ITT	Intent-to-treat
IV	Intravenous

Abbreviation	Term
KDIGO	Kidney Disease Improving Global Outcomes
LAR	Legally authorized representative
mITT	Modified intent-to-treat
OR	Odds ratio
PCC	Prothrombin complex concentrate
PP	Per-protocol
PROMMTT	Prospective Observational Multicenter Major Trauma Transfusion
PROPPR	Pragmatic Randomized Optimal Platelet and Plasma Ratios
RABT	Revised Assessment of Bleeding and Transfusion
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Steering Committee
TEE	Thromboembolic event
US	United States
VKA	Vitamin K antagonist

1 Introduction

1.1 Background

In the United States (US), accidents (ie, unintentional injuries, including trauma) were the leading cause of mortality in children, adolescents, and young adults aged 1 to 44 years between 1981 and 2019 [CDC, 2021]. According to the US Centers for Disease Control and Prevention (CDC), more than 240,000 fatal injuries occurred in 2019 in the US [CDC, 2020]. Additionally, trauma is a significant economic burden in terms of medical expenses and work-loss costs.

Hemorrhage is the most common, preventable cause of death following trauma. Mortality due to hemorrhage can reach as high as 40% in severely injured patients despite resuscitation efforts [Curry et al, 2011]. Hemorrhagic death occurs rapidly with a median time to death of 2 to 3 hours after hospital arrival [Holcomb et al, 2013; Holcomb et al, 2015]. Trauma patients on the verge of exsanguination have a unique pattern of physiologic derangements, collectively referred to as the lethal triad: hypothermia, metabolic acidosis, and coagulopathy [Holcomb et al, 2007; Hess et al, 2008]. Hemorrhage control, in combination with treatment of shock and balanced resuscitation, greatly reduces mortality in trauma patients [Spahn et al, 2019; Holcomb et al, 2015]. However, the optimal therapy is still not known.

Trauma transfusion care has changed dramatically over the past 20 years. This change was precipitated by the discovery of acute traumatic coagulopathy and endotheliopathy, and by the need to prevent and treat devastating complications of acute blood loss. The easiest way to do this is to replace “like-with-like”: blood lost from injuries should be replaced with blood containing the correct amounts of red cells, platelets, coagulation factors, and other components essential to achieving hemostasis.

The most common approach to trauma transfusion involves a formula or ratio-based approach, until the results of laboratory values become available, to guide the administration of specific products [Johannsen et al, 2021]. The spectrum of practice ranges from: (1) a ratio of one unit of plasma and / or platelets for every two units of red cells; (2) approximately equal ratios of units of plasma, platelets, and red cells; (3) some whole blood plus some components transfused at a ratio of 1:1:1 to 1:1:2; to (4) “whole blood only” (which only a handful of hospitals can provide).

There is still a critical need for improved methods to control bleeding in these patients. Even with the transfusion of the higher blood component ratio, the “Pragmatic, Randomized

Optimal Platelet and Plasma Ratios" (PROPPR) study found that hemorrhagic deaths occurred in 9.2% of patients [Holcomb et al, 2015]. This result has accurately predicted real-world results, namely, that exsanguination continues to be a leading cause of traumatic mortality and even best practices have only reduced hemorrhagic deaths by 25 to 30% [Johannsen et al, 2021; Oyeniyi et al, 2017]. Hence, an improved approach to control hemorrhage is an important unmet need.

A recently published systematic review and meta-analysis evaluated the effectiveness of prothrombin complex concentrate (PCC) administration in the treatment of bleeding in patients not taking anticoagulants in trauma, cardiac surgery, and liver surgery [Van den Brink et al, 2020]. From 4668 studies identified, 17 observational studies were included. In the trauma subgroup, mortality was significantly reduced in patients receiving PCC compared with patients not receiving PCC (odds ratio [OR] 0.64; confidence interval [CI] [0.46, 0.88]; $P = 0.007$; $I^2 = 0\%$; P for heterogeneity = 0.81). This benefit was observed when PCC was added to fresh frozen plasma (FFP) compared with FFP alone, but not when PCC as a stand-alone therapy was compared with FFP. Additionally, in trauma patients, PCC use resulted in a reduction of 3.0 red blood cell (RBC) units compared with patients not receiving PCC (95% CI [-4.1, -1.9]; $P < 0.00001$; $I^2 = 68\%$; P for heterogeneity = 0.02). While encouraging, the primary studies included in the systematic review and meta-analysis were all observational, and thus subject to confounding.

Retrospective data show that 4-factor prothrombin complex concentrates (4F-PCCs) may be an effective therapy in trauma patients who are not on preinjury anticoagulants and irrespective of whether or not they have a coagulopathy [Zeeshan et al, 2019a; Zeeshan et al, 2019b]. In a propensity score matched analysis, Zeeshan et al. showed that 4F-PCC as an adjunct to FFP was associated with improved survival and reduction in transfusion requirements compared with FFP alone in resuscitation of severely injured trauma patients [Zeeshan et al, 2019b]. It is possible that the effects of 4F-PCC extend beyond coagulopathy reversal, perhaps by decreasing endotheliopathy [Pati et al, 2016].

1.2 Information on BE1116

BE1116 is a human plasma-derived, highly purified, heat-treated, virus-filtered, lyophilized, 4F-PCC product. It contains the vitamin K-dependent blood coagulation Factors II, VII, IX, and X (FII, FVII, FIX, and FX), as well as the anticoagulants Protein C and Protein S, and other proteins, and it represents a multimodal therapy that may be a safe and effective therapy

to achieve hemostasis in patients who have traumatic injury, with confirmed or suspected acute major bleeding and / or predicted to receive a large volume blood product transfusion.

The preparation is obtained from pooled human plasma of healthy donors. Only plasma that passes virus screening is used for production. After dissolution in the appropriate amount of solvent, BE1116 is administered by intravenous (IV) infusion.

BE1116 is registered under different trade names (eg, Kcentra®, Beriplex® P/N), and current marketing authorizations vary across regions. In the US, BE1116 is indicated for the urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonist (VKA) (eg, warfarin) therapy in adult patients with acute major bleeding or need for an urgent surgery / invasive procedure [CSL, 2018]. In the European Union, BE1116 is indicated for the treatment and perioperative prophylaxis of bleeding in acquired deficiency of the PCC factors, such as deficiency caused by treatment with VKAs, or in case of overdose of VKAs, when rapid correction of the deficiency is required, and the treatment and perioperative prophylaxis of bleeding in congenital deficiency of any of the vitamin K-dependent coagulation factors when purified specific coagulation factor products are not available [CSL, 2021].

An extensive nonclinical program supports the use of BE1116 in patients who are deficient of vitamin K-dependent factors experiencing major bleeding or requiring urgent surgery, with the main cause of acquired factor deficiency being anticoagulation with VKA. To support the use of BE1116 in the new proposed indication, additional pharmacological studies in clinically relevant animal models of hemodilutional coagulopathy and trauma were employed to demonstrate the efficacy and safety of BE1116 in situations associated with major blood loss. Overall, the nonclinical studies demonstrated efficacy to correct hemostasis at clinically relevant dose levels, adequate pharmacokinetic properties, and a favorable safety profile of BE1116.

In all uncontrolled and controlled clinical studies of acute VKA reversal performed to date (333 total subjects treated with BE1116), BE1116 has been considered safe and well tolerated. Over 20 years of postmarketing experience also supports the favorable safety profile of BE1116 established during the clinical studies. The safety and efficacy of BE1116 in children and adolescents has not yet been established in controlled clinical studies. Additionally, the safety of BE1116 for use in human pregnancy and during lactation has not been established.

A detailed description of BE1116 is provided in the investigator's brochure (IB) for BE1116. This includes all relevant nonclinical and clinical data, including data from more than 20 years of postmarketing experience, to provide comprehensive information to investigators and others involved in the proposed clinical study.

1.3 Study Overview

There is good preliminary clinical evidence for a potential therapeutic role of 4F-PCC in trauma patients to improve survival (see Section 1.1). Therefore, this phase 3, randomized, double-blind, placebo-controlled study has been designed to evaluate the efficacy and safety of BE1116 when administered early in subjects who have traumatic injury, with confirmed or suspected acute major bleeding and / or predicted to receive a large volume blood product transfusion (ie, a massive transfusion protocol setting).

In addition to the study site's standard resuscitation methods and protocol, a single IV infusion of investigational product (IP) (BE1116 or placebo) will be administered, starting within 90 minutes of arrival at the hospital. Efficacy and safety data will be collected for the primary hospitalization period, up to the time of death / hospital discharge / Day 30, whichever occurs first. If subject is discharged alive prior to 6 hours, then the subject will be followed up to assess 6-hour survival status, SAEs, and AESIs. Primary hospitalization is defined as the initial hospitalization following the trauma. The primary endpoint is all-cause mortality within 6 hours after randomization.

Details regarding the scientific rationale for the study design and selection of dose are provided in Section 3.3.

1.4 Potential Risks and Benefits

The following benefits and risks are of consideration in this study:

Benefits

1. **There is the potential for improved survival** in patients who have traumatic injury, with confirmed or suspected acute major bleeding and / or predicted to receive a large volume blood product transfusion.
2. **There is the potential for decreased transfusion of blood products**, including RBCs, FFP, whole blood, cryoprecipitate, intraoperative salvaged (cell-saver) blood, and platelets, with reduction of associated risks, eg, transfusion reactions including

transfusion-associated circulatory overload and transfusion-related acute lung injury or transmission of infectious agents [CSL, 2018].

3. **There is the potential for decreased complications**, including decreased length of stay in the intensive care unit (ICU) and hospital and decreased number of days on mechanical ventilation.

Risks

1. **There is an increased risk of acute thromboembolic events (TEEs)**, including deep vein thrombosis, pulmonary embolism, ischemic stroke [including thromboembolic stroke], and myocardial infarction within 24 to 48 hours after BE1116 administration [CSL, 2018].
2. **The concurrent use of off-label prothrombotic agents (eg, recombinant activated FVIIa, Factor VIII inhibitor bypassing activity [FEIBA]) may increase the risk of TEEs** [Novo Nordisk, 2020; Baxalta, 2020].
3. **Hypersensitivity reactions** may occur [CSL, 2018].
4. **There is a low risk of transmissible infectious agents** (the PCC manufacturing process applies 2 dedicated virus reduction steps) [CSL, 2018].

Thus, the anticipated benefit-risk balance of BE1116 is considered acceptable for subjects enrolled in the study.

Refer to the IB for BE1116 for detailed information on the product's warnings, precautions, and full safety profile.

2 Study Objectives and Endpoints

2.1 Primary Objective and Endpoint

2.1.1 Primary Objective

The primary objective is to assess the efficacy of a single IV infusion of BE1116 on all-cause mortality within 6 hours after randomization in subjects who have traumatic injury, with confirmed or suspected acute major bleeding and / or predicted to receive a large volume blood product transfusion.

2.1.2 Primary Endpoint

The primary endpoint is all-cause mortality within 6 hours after randomization.

2.1.3 Primary Estimand

The primary estimand to address the trial objective is the difference in proportion of all-cause mortality up to 6 hours after randomization (6-hour mortality) in subjects who have traumatic injury, with confirmed or suspected acute major bleeding and / or predicted to receive a large volume blood product transfusion (Intent-to-treat [ITT] Population) between the BE1116 and placebo arms, regardless of IP dosage received or other medications used. See Section 10.2.1 for a definition of the ITT Population.

The 4 attributes of the primary estimand (population, primary endpoint, intercurrent events [ICEs], and summary measure), as defined in the International Council for Harmonisation (ICH) E9 (R1) guidance, are described below.

2.1.3.1 Population

Subjects who have traumatic injury, with confirmed or suspected acute major bleeding and / or predicted to receive a large volume blood product transfusion (ITT Population).

2.1.3.2 Primary Endpoint

As defined in Section 2.1.2.

2.1.3.3 Intercurrent Events

2.1.3.4 Summary Measure

The summary measure of the primary endpoint is the difference in the proportion of subjects who die in hospital in the BE1116 arm compared with the placebo arm during the first 6 hours after randomization (see Section 2.1.1), as estimated by a Bayesian logistic regression model.

2.2 Secondary Objectives and Endpoints

2.2.1 Secondary Objectives

The secondary objectives of the study are as follows:

1. To assess all-cause in-hospital mortality up to 24 hours after randomization
2. To assess all-cause in-hospital mortality up to 30 days after randomization
3. To assess the requirement for surgical or interventional radiological procedures to stop bleeding related to the primary injury up to 24 hours after randomization
4. To assess the safety of BE1116

2.2.2 Secondary Endpoints

The secondary endpoints (and corresponding summary measures) of the study are as follows:

Secondary Objective	Endpoint	Summary Measure
1	All-cause in-hospital* mortality up to 24 hours after randomization	Difference in proportion of subjects who die in hospital in the BE1116 arm compared with the placebo arm up to the first 24 hours after randomization, as estimated by a Bayesian logistic regression model
2	All-cause in-hospital* mortality up to 30 days after randomization	Difference in proportion of subjects who die in hospital in the BE1116 arm compared with the placebo arm up to 30 days after randomization, as estimated by a Bayesian logistic regression model
3	Surgical or interventional radiological procedures to stop bleeding related to the primary injury up to 24 hours after randomization	Difference in proportion of subjects who undergo surgical or interventional radiological procedures to stop bleeding related to the primary injury in the BE1116 arm compared with the placebo arm up to 24 hours after randomization, as estimated by a Bayesian logistic regression model

Secondary Objective	Endpoint	Summary Measure
4	Serious adverse events (SAEs) considered related to IP	During the primary hospital stay only, within the 30 days after randomization: • Number and proportion of subjects with SAEs considered related to IP by treatment (BE1116 or placebo)
4	Adverse events of special interest (AESIs): • TEEs, symptomatic or asymptomatic, and arterial or venous (eg, deep vein thrombosis, pulmonary embolism, ischemic stroke [including thromboembolic stroke], myocardial infarction) • Acute respiratory distress syndrome (ARDS) • Multiple organ failure • Acute kidney injury (AKI) requiring renal replacement therapy (dialysis, hemofiltration, or hemodiafiltration) **Note**: superficial thromboses will not be included as AESIs	• TEEs: Number and proportion of in-hospital overall and related TEEs up to 30 days after randomization by treatment (BE1116 or placebo) • Number and proportion of subjects with the following: o ARDS o Multiple organ failure o AKI requiring renal replacement therapy

*In-hospital mortality will only be recorded and assessed for the primary hospitalization.

2.3 Exploratory Objectives and Endpoints

2.3.1 Exploratory Objectives

The exploratory objectives of the study are as follows:

1. To assess transfusion of blood products
2. To assess healthcare utilization during primary hospitalization

2.3.2 Exploratory Endpoints

The exploratory endpoints (and corresponding summary measures) of the study are as follows:

Exploratory Objective	Endpoint	Summary Measure
1	Transfusion of blood products	Number of units of blood products transfused before arrival at the hospital through the first 24 hours after randomization, overall and by type of product by treatment
2	Ventilator-free days	Number of ventilator-free days during the primary hospital stay up to 30 days after randomization, by treatment
2	ICU-free days	Number of ICU-free days during the primary hospital stay up to 30 days after randomization, by treatment
2	Hospital length of stay	Number of days of primary hospitalization

Details regarding how the exploratory endpoints will be calculated and adjusted for deaths will be provided in the statistical analysis plan (SAP).

3 Study Design and Oversight

3.1 Overall Design

This is a phase 3, prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group, large simple trial to investigate the efficacy and safety of a single IV infusion of BE1116 in subjects who have traumatic injury, with confirmed or suspected acute major bleeding and / or predicted to receive a large volume blood product transfusion.

The IP infusion will be given in addition to the study site's standard resuscitation methods and protocol. All subjects will receive standard of care according to the study site's normal clinical practice at all times during the study. Standard-of-care should not be interrupted or forgone to enable subject participation in the study.

Randomization will be in a 1:1 ratio (BE1116:placebo) and stratified by study site. The time of randomization is defined as the time at which the selected IP study kit is opened by the trauma team (or other applicable site staff) for IP reconstitution and administration.

The study will be conducted at approximately 140 sites in the US and other countries with emergency medical services, trauma systems, in-hospital trauma teams, and resuscitation protocols. All participating study sites will be Level I or Level II trauma centers (or equivalent) that have a large number of patients and an existing, robust research infrastructure to support this trial. Level I trauma centers are defined as a comprehensive regional resource that is in a tertiary care facility, central to the trauma system, and capable of providing definitive care for every aspect of injury – from prevention through rehabilitation. Level II trauma centers are able to initiate definitive care for all injured patients [American Trauma Society, 2021]. Participating sites will deliver a contemporary balanced standard of transfusion care ("balanced resuscitation") to ensure no confounding of results from differences in standard-of-care practices.

The study consists of: (i) a Screening and Randomization (Enrollment) Period; (ii) a Treatment Period; and (iii) an In-hospital Follow-up Period, as summarized below. An overview of the study is shown in Figure 1. Further details regarding the assessments performed in each period are provided in Section 8.5.

Screening and Randomization (Enrollment) Period

Screening will begin once the subject has arrived at the hospital, and eligibility will be assessed. This study involves subjects who cannot be prospectively identified and who have life-threatening medical conditions necessitating emergent intervention. Because of the subjects' conditions, the emergent need for intervention, and the limited treatment window during which the IP must be administered for potential efficacy, it is anticipated that obtaining prospective Informed Consent (as defined in Appendix 8) from study subjects or their Legally Acceptable Representatives (as defined in Appendix 8) may not be possible. For these reasons, the study will be conducted under emergency research Applicable Law (as defined in Appendix 8) which allows subjects to be enrolled into qualifying research without obtaining prospective Informed Consent. For details regarding Informed Consent, refer to Section 12.3 and Section 12.3.1.

Once a subject meets all the eligibility criteria, the trauma team (or other applicable site staff) will select and open the IP study kit (for IP reconstitution and administration) with the next

available sequential subject number, and the subject will be considered randomized (enrolled). The date and time of opening the IP study kit (randomization) will be recorded.

Treatment Period

The start of the IP infusion must be within 90 minutes after arrival at the hospital.

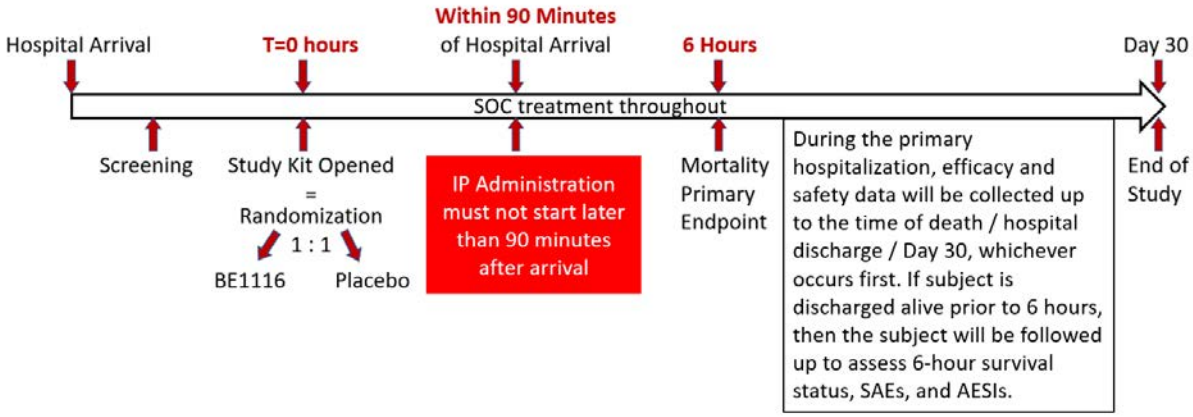
Blinded, sealed IP study kits containing either BE1116 or placebo will be maintained in the trauma bay, or a location where they are readily accessible, at the study site at all times during the study.

In-hospital Follow-up Period

During the primary hospitalization, efficacy and safety data will be collected up to the time of death / hospital discharge / Day 30, whichever occurs first. If subject is discharged alive prior to 6 hours, then the subject will be followed up to assess 6-hour survival status, SAEs, and AESIs.

For details regarding Informed Consent, refer to Section 12.3 and Section 12.3.1.

Figure 1 Study Overview



AESI = adverse event of special interest; IP = investigational product; SAE = serious adverse event; SOC = standard-of-care, T = time.

Notes: Time = 0 hours is the time of opening the IP study kit (randomization). The start of the IP infusion must be within 90 minutes after arrival at the hospital.

3.2 Dose and Dosing Regimen

Subjects will receive a single IV infusion of either BE1116 or placebo, in addition to the study site's standard resuscitation methods and protocol.

The dose of BE1116 will be either 2000 IU or 3000 IU, based on the estimated or measured weight of the subject documented on arrival at the hospital:

- Weight < 75 kg (< 165 lbs): 2000 IU
- Weight ≥ 75 kg (≥ 165 lbs): 3000 IU

Details regarding dose administration are provided in Section 5.1.3.

3.3 Scientific Rationale

3.3.1 Study Design Rationale

This study has been designed to assess the efficacy and safety of BE1116 in subjects who have traumatic injury, with confirmed or suspected acute major bleeding and / or predicted to receive a large volume blood product transfusion.

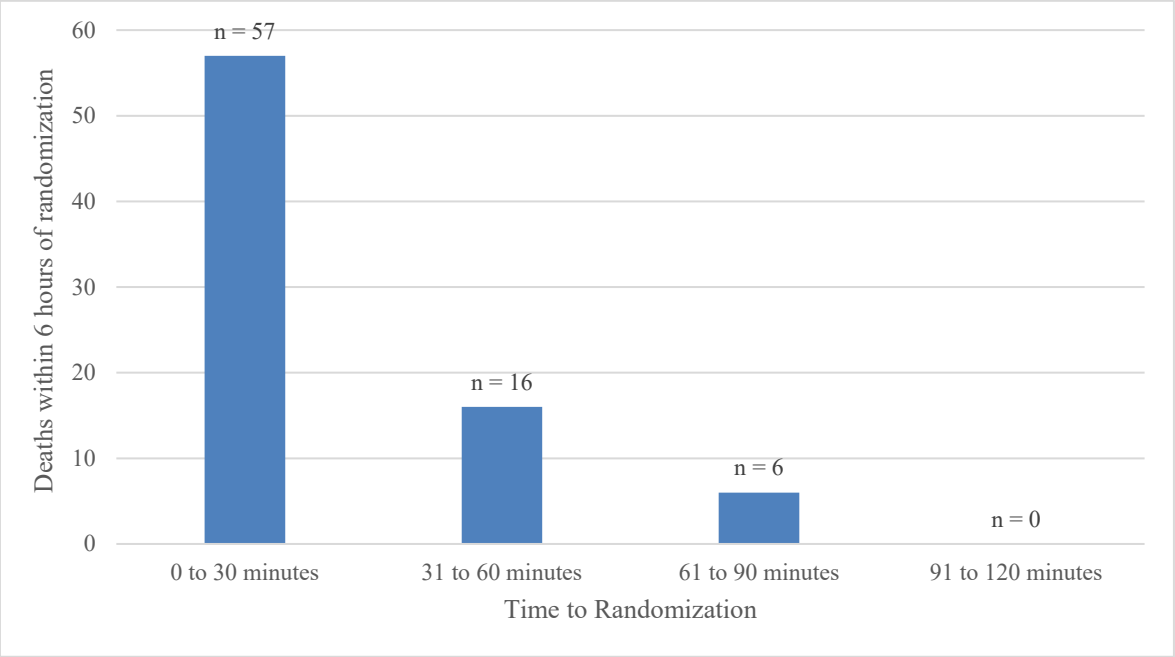
A randomized, double-blind, placebo-controlled design was considered appropriate to reduce bias. Placebo was chosen as the comparator because no licensed treatment is currently available for the indication under study. The study IP (BE1116 or placebo) will be administered in addition to the study site's standard resuscitation methods and protocol (also referred to as "standard-of-care"). This will ensure that adequate treatment is given to subjects in both treatment arms, according to current treatment algorithms in this emergency setting. The study is pragmatic, there will not be a prescribed uniform resuscitation protocol employed by all study sites; thus, the study will reflect real-world practice. However, participating sites will deliver a contemporary balanced standard of transfusion care ("balanced resuscitation") to ensure no confounding of results from differences in standard-of-care practices.

This study involves subjects who cannot be prospectively identified and who have life-threatening medical conditions necessitating emergent intervention. Because of the subjects' conditions, the emergent need for intervention, and the limited treatment window during which the IP must be administered for potential efficacy, it is anticipated that obtaining prospective Informed Consent from subjects or their Legally Acceptable Representatives may not be possible. For these reasons, the study will be conducted under

emergency research Applicable Law which allows subjects to be enrolled into qualifying research without obtaining prospective Informed Consent. This trial is designed to test whether early administration of BE1116 will reduce mortality in subjects with uncontrolled hemorrhage. The natural history of uncontrolled hemorrhage is of falling cardiac output and hypotension and ultimately failure of compensatory mechanisms with consequent cerebral and myocardial hypoperfusion leading to death [Peitzman et al, 1995]. The therapeutic window for exsanguinating trauma patients is short – often only minutes. It is imperative that BE1116 or placebo be administered rapidly and no later than 90 minutes from arrival in the trauma center [Abraham et al, 2022] for the following reasons:

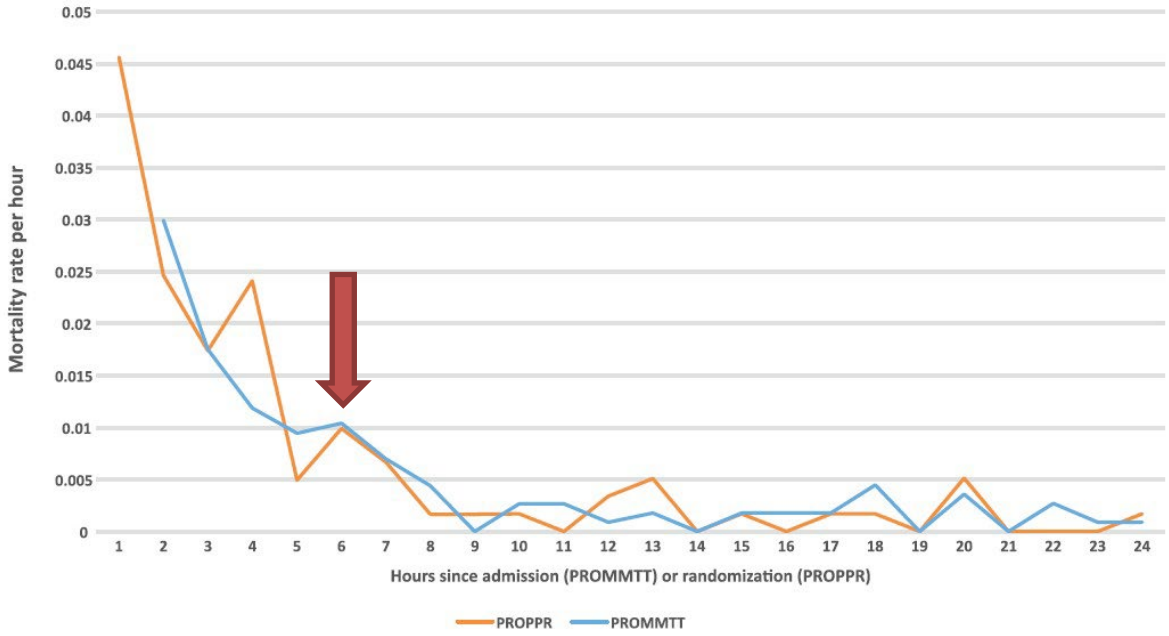
1. *Deaths from hemorrhage occur early*. An analysis of 42,135 patients with torso injury and hypotension showed that the majority of deaths occur within 30 minutes of injury [Alarhayem et al, 2016]. Harvin et al [2017] recently described the outcome of 1706 patients requiring trauma laparotomy within 90 minutes of hospital arrival at 12 Level I trauma centers. In patients who were hypotensive on admission, 41% of deaths occurred within 1 hour of arrival in the emergency department.
2. *Patients enrolled within 90 minutes of arrival have higher mortality than those enrolled later*. A further analysis of the PROPPR study has shown that patients who were enrolled within 90 minutes of arrival at the trauma center had a high risk of early death (within 24 hours), whereas none of the patients who were enrolled after 90 minutes died early [Abraham et al, 2022] (Figure 2).

Figure 2 **All-cause 6-Hour Mortality Decreases With Time to Randomization (N = 677)**



The primary study endpoint is all-cause mortality within 6 hours after randomization. This reflects the physiology and time course of hemorrhagic death, and the biology of the intervention. Trauma deaths from hemorrhage occur early, within hours of the injury, and if BE1116 has a beneficial effect, it is most likely to occur during this phase of treatment. Later deaths are usually due to other causes, such as traumatic brain injury, sepsis, or multiple organ failure and are therefore unlikely to be impacted by treatment with BE1116, targeted at aiding hemostasis [Holcomb et al, 2013; Tisherman et al, 2015; Fox et al, 2017; Herrera-Escobar et al, 2018; Holcomb et al, 2021; Spinella et al, 2021]. Hourly mortality rates from the PRospective Observational Multicenter Major Trauma Transfusion (PROMMTT) and PROPPR studies, which assessed hemorrhagic deaths following trauma, are provided in Figure 3. These show that the 6-hour time point for all-cause mortality aligns with the expected time of death due to hemorrhage and the time frame to detect an effect of the experimental intervention.

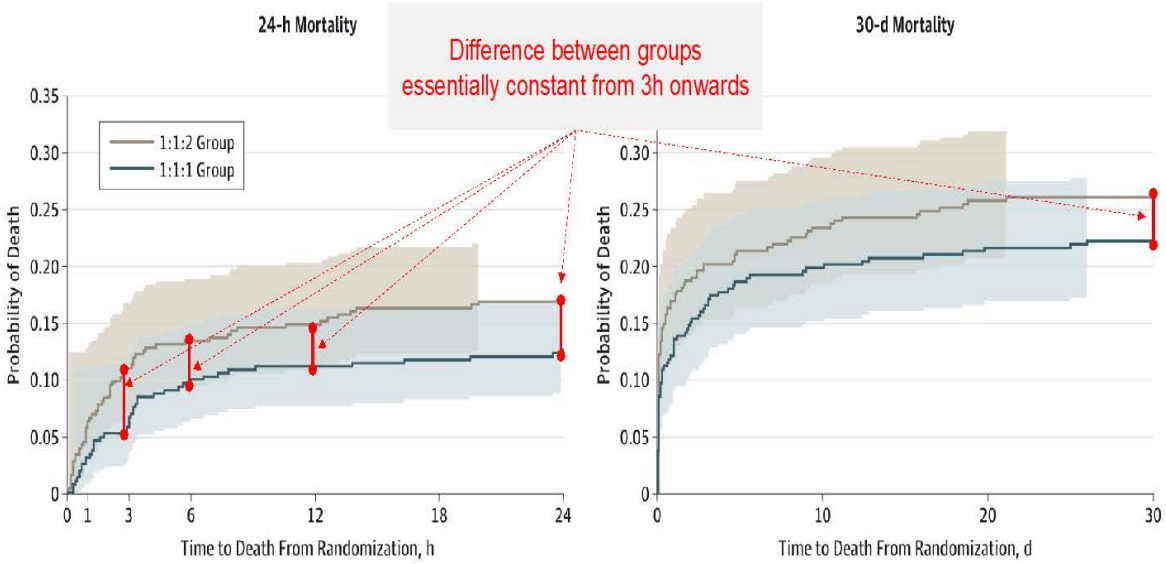
Figure 3 Hourly Mortality Rates From PROMMTT and PROPPR Studies



PROMMTT = PRospective Observational Multicenter Major Trauma Transfusion (study);
PROPPR = Pragmatic Randomized Optimal Platelet and Plasma Ratios (study)
Source: Figure 1 in [Fox et al, 2017].

Importantly, prior similar studies have shown that mortality differences present in the first few hours persist over the next 30 days. The PROPPR study [Holcomb et al, 2015] was sponsored by the US National Institutes of Health (NCT01545232). The study compared a 1:1:1 and a 1:1:2 transfusion ratio (of units of thawed plasma:platelets:red cells) and showed that mortality differences between the 2 treatment arms were already apparent at 3 hours post-randomization, and the absolute difference remained the same at the 30-day time point, as shown by the Kaplan-Meier curves in Figure 4. Likewise, the Prehospital Air Medical Plasma (PAMPer) study that found a benefit of prehospital administration of plasma at 3 hours that persisted 30 days [Sperry et al, 2018].

Figure 4 **Kaplan-Meier Plots of 24-hour and 30-day Mortality: Difference Between Groups Maintained From 3 Hours Onwards**



Source: [Holcomb et al, 2015]

While the relative mortality trends in the first 6 hours will likely persist over time in the current study, secondary efficacy endpoints include all-cause in-hospital mortality up to 24 hours after randomization, and all-cause in-hospital mortality up to 30 days after randomization. These will reflect the durability of survival benefit, provide valuable safety information about later mortality and relevant complications, and are in line with other trauma studies, such as the PROPPR study [Holcomb et al, 2015; Fox et al, 2017]. An earlier time to hemostasis was found to be independently associated with a decreased incidence of 30-day mortality, AKI, ARDS, multiple organ failure, and sepsis in 408 bleeding trauma patients, indicating that the benefits of an earlier time to hemostasis are reflected in a number of outcomes, including mortality up to 30 days [Chang et al, 2019].

Safety data collected in the in-hospital period after randomization (up to the time of death, hospital discharge, or 30 days, whichever occurs first; if subject is discharged alive prior to 6 hours, then the subject will be followed up to assess 6-hour survival status, SAEs, and AESIs) will allow the monitoring of AESIs and SAEs, which will be assessed for relatedness to the IP. TEEs are a defined AESI in this study because they are an identified important risk associated with use of BE1116. The other AESIs (ARDS, multiple organ failure, and AKI requiring renal replacement therapy) have been selected based on their importance in trauma

study populations. Nonserious adverse events (AEs) (other than AESIs) will not be collected in this study, because BE1116 has an established safety profile from more than 20 years of postmarketing experience in more than 45 countries, as well as from 10 clinical studies. In the current study, there will be a short duration of exposure (single dose), and the dosing range falls within that used in current clinical practice and in previous clinical studies.

The design will be of a "large simple trial". Large simple trials have been proposed by academia, industry, and regulatory authorities as an option to investigate interventions that are expected to show moderate, albeit clinically meaningful, improvements in the standard of care. The clinical meaningful outcome of interest of this trial is mortality. Even small improvements in mortality are highly relevant. The Clinical Trials Transformation Initiative, a public / private partnership founded by the US Food and Drug Administration (FDA) and Duke University (Durham, North Carolina, US) in 2013, convened a working group in May 2013. The group concluded that: large simple trials are helpful when moderate treatment effects are anticipated; they should have clinical, rather than surrogate, endpoints; they require streamlined data collection; and, for most therapies, they should be randomized [Eapen et al, 2014]. In line with these conclusions, this clinical trial: 1) has a large sample size with an objective, clinically meaningful primary endpoint of all-cause 6-hour mortality; 2) limits data collection to that required to analyze the study endpoints; and, 3) is randomized.

Analysis of the primary endpoint will be conducted with a Bayesian logistic regression model within a group sequential framework with three interim analyses planned. The study may be stopped early if futility (nonbinding) criteria are met at any of the three planned interim analyses, or if efficacy criteria are met at Interim Analysis 2 or 3. Trauma experts have recommended Bayesian models for analysis and to facilitate interpretation and easy translation of results into clinical practice of hemostasis research among clinicians [Jansen et al, 2017]. Furthermore, the Bayesian concept of posterior predictive probability presents a robust strategy to monitor futility while accounting for data remaining to be observed in the trial [Saville et al, 2014].

An Independent Data Monitoring Committee (IDMC) will also review results periodically during the study and will provide recommendations (see Section 3.8.1). An Executive Committee (EC) will provide oversight for the operation of the study (see Section 3.8.2).

Rationale regarding the study population is provided with the inclusion and exclusion criteria in Section 4.1.

3.3.2 Dose Rationale

For the current study, a dose of BE1116 within the approved range for warfarin reversal of 25 to 50 IU/kg will be tested. As a single dose range in trauma is unknown, and there is not a single dose that could be administered to all subjects, 2 weight-dependent doses will be administered in this study: 2000 IU and 3000 IU. Either estimated or actual (measured) weight may be used. This dichotomized approach is also pragmatic, which is helpful in the context of the pressured trauma clinical setting. Study staff will be able to reconstitute and administer the IP quickly without the need for weight-based calculations.

Subjects with a body weight of < 75 kg (< 165 lbs) will receive a single dose of 2000 IU BE1116 (or matching placebo). It is expected that this dose will not exceed 50 IU/kg, because subjects would need to have a body weight of < 40 kg (< 88 lbs) to reach doses above 50 IU/kg. The eligibility criteria will exclude subjects with a body weight of < 50 kg (< 110 lbs).

Subjects with a body weight of ≥ 75 kg (≥ 165 lbs) will receive a single dose of 3000 IU BE1116 (or matching placebo). This is equivalent to a 40 IU/kg maximum dose for the lowest body weight (75 kg). To reach doses outside the currently approved 50 IU/kg, with a single dose of 3000 IU, the actual weight would need to be ≤ 60 kg (≤ 132 lbs).

A pharmacokinetic analysis in 15 healthy volunteers who received an infusion of 50 IU/kg (at approximately 200 IU/min) resulted in an early peak of factor increase after 5 minutes. No increase in thrombogenicity marker (D-Dimer) was observed, and no clinical signs of thrombosis could be detected [Ostermann et al, 2007].

Details regarding dosing are provided in Section 5.1.3.

3.4 Planned Study Duration

The study duration for an individual subject who dies while on the study is up to the time of death. For other subjects, the study duration is at least 6 hours and ends with hospital discharge, or 30 days, whichever comes first. If subject is discharged alive prior to 6 hours, then the subject will be followed up to assess 6-hour survival status, SAEs, and AESIs.

Time: 0 to 90 minutes after hospital arrival:

- Screening
- Randomization (enrollment)
- Start of IP infusion

Time: 0 to 30 days post-randomization:

- Subjects will be followed up until death / hospital discharge / Day 30, whichever occurs first. If subject is discharged alive prior to 6 hours, then the subject will be followed up to assess 6-hour survival status, SAEs, and AESIs.

The overall study duration (ie, from screening of first subject through the end of the last subject's In-hospital Follow-up Period) will be approximately 3 years.

3.5 Planned Number of Subjects

It is planned to enroll up to 8000 subjects (4000 per treatment arm). See Section 10.1 for further details on sample size.

3.6 Definition of Start of the Clinical Study

The start of the clinical study is defined as the date of the first act of screening a potential subject at a study site.

3.7 Definition of End of the Clinical Study

The end of the clinical trial (ie, completion of the study at all participating study sites) is defined as the date of the last subject's death / hospital discharge / Day 30, whichever occurs first. If subject is discharged alive prior to 6 hours, then the subject will be followed up to assess 6-hour survival status, SAEs, and AESIs.

3.8 Study Oversight

3.8.1 Independent Data Monitoring Committee

An IDMC will be established by CSL Behring (CSL), consisting of 1 chairperson, 1 statistician, 2 clinical experts, and 1 bioethicist with a robust background in clinical studies.

The IDMC will be established prior to enrollment of the first subject. Members of the IDMC will be external to CSL and should have the expertise in the field needed on the committee,

and independence from the direct ability to influence the clinical study. IDMC members may include a hematologist with experience in transfusion medicine, a trauma surgeon, an emergency medicine physician, a biostatistician, and a bioethicist. No members are to have financial or personal conflicts of interest, to ensure that the data are reviewed in an unbiased manner. The chairperson should confirm before each meeting that no member has any new conflict of interest related to the function of the IDMC.

The IDMC will review relevant data, including safety data per treatment arm, periodically during the study and at least semi-annually, depending on the speed of recruitment. Ad-hoc meetings may be scheduled as required.

The IDMC will monitor unblinded, death, AEs including SAEs and AESIs, as well as other safety data, with the objective of ensuring the safety of study subjects.

The IDMC will provide recommendations on the continuation, modification, or termination of the study based on interim analysis and / or review of safety / efficacy data as described in Section 10.3.4. The IDMC may recommend temporarily or permanently stopping the study if BE1116 has a significantly higher safety risk compared with placebo. The IDMC recommendations will be relayed to CSL for final decision making.

If a safety assessment concludes that a substantial protocol amendment (eg, additional risk mitigation measures) is required, the study will be paused until the protocol has been revised and accepted by the relevant regulatory authorities and Institutional Review Boards (IRBs) / Independent Ethics Committees (IECs). CSL will provide written communication of the decision from the safety assessment and instructions to the participating investigator sites in a timely manner.

If the IDMC recommends and CSL decides that any additional dosing poses an unacceptable risk to subjects and no further risk mitigation steps can be applied, the study will be terminated.

Relevant regulatory authorities and IRBs / IECs will be informed in accordance with local requirements, and all subjects that were dosed will be followed according to the scheduled study visits for safety.

Further details on the composition, responsibilities, meeting schedule, data for review, recommendations of the IDMC, and stopping rules for the study are described in Section 10.3.4 and the IDMC Charter.

3.8.2 Executive Committee

An EC will be established to review and provide guidance and recommendations to CSL relating to the medical and scientific conduct of the study.

The EC will be composed of members of the academic leadership of the clinical study and members of CSL. The EC will provide oversight for the operation of the study, including working with national leaders and local study site investigators to achieve goals for enrollment of subjects into the study, reviewing recommendations from the project team for study conduct, and reviewing recommendations from the IDMC for subject safety.

Further details on the composition, responsibilities, meeting schedule, data for review, and recommendations of the EC will be described in an EC Charter.

3.8.3 Steering Committee

A Steering Committee (SC) will be established to provide feedback to the Sponsor on ongoing study site activities and help facilitate communication with study sites regarding enrollment and conduct of the study. The SC will be composed of members of the academic leadership of the clinical study, study site principal investigators, and members of CSL. The SC will report to the EC. Further details on the composition, responsibilities, and meeting schedule of the SC will be described in an SC Charter.

3.8.4 Publications Committee

A Publications Committee will be established to facilitate, encourage, and coordinate dissemination of results and analyses of Study BE1116_3006. Further details will be described in the Publications Committee Charter.

3.8.5 Stopping Criteria

The study may be stopped early if futility (nonbinding) criteria are met at any of the three planned interim analyses, or if efficacy criteria are met at Interim Analysis 2 or 3, as described in Section 10.3.2.1 and Section 10.3.4. In addition, based on continuous safety monitoring, the study can be temporarily halted, modified via a protocol amendment, or terminated per the following.

The IDMC will review and then decide if the assessment requires a cumulative review of the cases of in-hospital TEEs, in-hospital SAEs with a fatal outcome, and other safety data. In

addition, the IDMC will conduct periodic cumulative reviews of all in-hospital SAEs with a fatal outcome and all in-hospital TEEs and other in-hospital AESIs, as defined in the IDMC Charter.

Specific stopping rules for the above-mentioned safety signals are elaborated in Section 10.3.4, the IDMC Charter, and the SAP.

Discontinuation of study treatment and subject withdrawal is described in Section 4.3. Study and site closure is described in Section 13.6.

4 Selection and Withdrawal of Subjects

4.1 Eligibility Criteria

The study population will be selected based on the inclusion and exclusion criteria described in the sections below. Subjects must meet all inclusion criteria and none of the exclusion criteria at the time of randomization (enrollment) to be eligible for this study. Prospective approval of protocol deviations from eligibility criteria, also known as protocol waivers or exemptions, is not permitted. Subject eligibility should be reviewed and documented by an appropriately medically qualified member of the investigator's study team before subjects are included in the study.

Criteria that were changed in Protocol Amendment 1 are identified by the addition of "A1" in the numbering. Criteria that were changed in Protocol Amendment 2 are identified by the addition of "A2" in the numbering.

4.1.1 Inclusion Criteria

To be enrolled into the study, subjects must meet all of the following inclusion criteria:

Inclusion Criterion	Rationale
1.A2. (a) Estimated or actual age ≥ 15 years. Older minimum age is required in some locations. *FOR United Kingdom*: Estimated or actual age ≥ 16 years *FOR Australia*: Estimated or actual age ≥ 18 years	Subjects with an age ≥ 15 years globally are included in this study when in compliance with Applicable Laws, because trauma is the leading cause of mortality in the US among children, adolescents, and adults aged 1 to 44 years (see Section 1.1). Up to 20% of trauma subjects may be < 18 years of age. In the US, older injured children are generally cared for in adult trauma centers, although the threshold varies. Also, older adolescents aged ≥ 15 years are

Inclusion Criterion	Rationale
AND (b) Estimated or actual weight ≥ 50 kg (110 lbs).	physiologically comparable to young adults in the development of their coagulation system and response to trauma and shock [Liras et al, 2016]. In the setting of this study, it may not be possible to determine the subject's age upon arrival at the hospital if no identification is available, especially if urgent treatment is required. A lower weight limit is included to limit enrollment of subjects aged < 15 years (for example, when age is estimated) and per the dose calculation considerations to demonstrate that that the dose would fall into the Sponsor's known and studied dose range and to decrease the risk of overdose (Section 3.3.2). A higher minimum age is in effect for some jurisdictions, including United Kingdom and Australia, to be in compliance with Applicable Laws. No specific safety data exist for BE1116 use in the 15- to 17-year-old age group, but no additional risks are expected compared with subjects aged ≥ 18 years.
2.A1. Traumatic injury with: (a) confirmed or suspected acute major bleeding; and / or (b) Revised Assessment of Bleeding and Transfusion (RABT) score ≥ 2.	Indication under investigation. A retrospective analysis found that a RABT score ≥ 2 had a sensitivity of 84% and specificity of 77% for predicting massive transfusion [Joseph et al, 2018].
3.A1. Not applicable.	Deleted at Global Amendment 1.
4. Activation of massive transfusion protocol.	To ensure injury severity, corresponds to indication under study.
5.A2. Initiation of blood product transfusion (Whole Blood or RBCs or Platelets or Plasma has started to enter patient's body).	To ensure injury severity, corresponds to indication under study.
6.A1. Anticipated start of IP infusion within 90 minutes after arrival at the hospital.	To ensure homogenous study population, known to be at high risk of early death.

Table 1 RABT Variables and Scoring

RABT Variables	Score	Notes
Positive FAST	1 = yes, 0 = no	
Shock index > 1	1 = yes, 0 = no	Shock index = ratio of heart rate to systolic blood pressure, ie, heart rate / systolic blood pressure
Presence of a pelvic fracture	1 = yes, 0 = no	
Penetrating mechanism of injury	1 = yes, 0 = no	

FAST = Focused Assessment for the Sonography of Trauma examination; RABT = Revised Assessment of Bleeding and Transfusion.

4.1.2 Exclusion Criteria

Subjects must not be enrolled into the study if they meet any of the following exclusion criteria:

	Exclusion Criteria	Rationale
1.A2.	Healthcare professional cardiopulmonary resuscitation including chest compressions for ≥ 5 consecutive minutes at any time before randomization.	Very high probability of death and morbidity, unlikely to survive.
2.	Isolated penetrating or blunt cranial injury, or exposed brain matter.	Very high probability of death and morbidity related to traumatic brain injury and not related to acute major bleeding.
3.	Known anticoagulation treatment or a history of a TEE, within the past 3 months.	Subject population could confound results and / or pose a safety risk.
4.A1.	Isolated burns estimated to be > 20% total body surface area or suspected inhalational injury.	Significant total body surface area burns or smoke inhalation will influence coagulopathy and blood product administration.
5.	Ground level fall.	Likely traumatic brain injury and not hemorrhagic shock due to trauma [Schreiber et al, 2015].
6.	Drowning or hanging.	Non-traumatic hypoxic / anoxic injury.

	Exclusion Criteria	Rationale
7.	Subject transferred from another hospital.	Subject population likely to have received care before arrival at the hospital and / or spent time at another institution that could confound results. Subjects who were transported en route through, but did not enter, another institution are permitted if they did not receive care (eg, subject transferred from ambulance to helicopter).
8.	Known heparin-induced thrombocytopenia.	Known heparin-induced thrombocytopenia. BE1116 contains heparin [CSL, 2018].
9.	Known hereditary disorders that significantly increase prothrombotic risk such as hereditary antithrombin III deficiency, Factor V Leiden, etc.	There is an increased risk of TEE associated with these underlying conditions that may confound safety data from BE1116 administration.
10.	Known or suspected pregnancy.	There are no data with BE1116 use in pregnancy to inform on drug-associated risk [CSL, 2018].
11.	Known anaphylactic or severe systemic reactions to BE1116 or any components in BE1116 including heparin, Factors II, VII, IX, X, Proteins C and S, antithrombin III, and human albumin.	Known anaphylactic or severe systemic reactions to BE1116 or any components in BE1116 including heparin, Factors II, VII, IX, X, Proteins C and S, antithrombin III and human albumin [CSL, 2018].
12.A2.	Known prisoner at time of enrollment.	Vulnerable population.
13.	Known "Do Not Resuscitate" order.	Subject's explicit wish must be respected.
14.A2.	(a) *FOR all study sites*: Subject or Legally Acceptable Representative voiced an objection to participation in the trial **OR** (b) *FOR United States*: A family member voiced an objection to participation in the trial or subject was wearing an "opt-out" bracelet.	a. A patient with mental capacity should be granted full autonomy to object to study participation. If the subject lacks mental capacity, then an available Legally Acceptable Representative has the right to object on the potential subject's behalf. b. In the United States, family members have the right to object to trial participation. Potential subjects wearing an "opt-out" bracelet will have previously opted out of the study during the community education procedure.

Exclusion Criteria	Rationale
15.A1. Known participation in another interventional clinical study except with prior documented agreement from the sponsors.	Subjects receiving other investigational products may confound outcomes. However, participation in some studies may not prejudice subject safety or data integrity, so subjects enrolled in another study may participate in both if the site principal investigator obtains agreement from the sponsors of both studies in advance.
16.A1. Known treatment with any prohibited medications including 3F-PCC, 4F-PCC, aPCC (FEIBA), and / or Factor VIIa after trauma and prior to randomization.	Administering 1 of these drugs and IP may confound primary endpoint and safety signals.
17.A2. Normal level of consciousness (Glasgow Coma Scale score of 15).	Level of consciousness is a subtle marker of cerebral perfusion. A normal level of consciousness indicates that the patient is unlikely to be in shock and thus unlikely to benefit from BE1116.
18.A2. Moribund patient with devastating injuries expected to die within 1 hour of hospital arrival.	Patients that have virtually no chance of survival do not have potential to benefit from BE1116.

4.2 Screen Failures

Screen failures are defined as individuals who are screened but do not meet the eligibility criteria for participation in the study. There is no requirement to collect data from screen failures in this study.

4.3 Discontinuation of Study Treatment and Subject Withdrawal

4.3.1 Discontinuation of Study Treatment

This is a single-dose study. Discontinuation of the IP infusion is not expected.

IP infusion may be stopped for medical reasons due to safety issues (eg, if pregnancy is confirmed for a subject).

If a subject declines further study procedures, the subject will be withdrawn from the study. Refer to Sections 4.3.2 and 4.3.3 for details on handling subject withdrawals.

4.3.2 Subject Withdrawal

Subjects may withdraw from the study at any time at their own request (or that of their Legally Acceptable Representative, if applicable), or at the discretion of the investigator or CSL for safety, behavioral or administrative reasons (eg, because of an AE, protocol deviation, loss to follow-up, subject noncompliance, study termination). The investigator should record the reason and date of subject withdrawal in the electronic case report form (eCRF) and in the subject's medical records.

In accordance with the ICH principles of Good Clinical Practice (GCP), the investigator always has the option to advise a subject to withdraw from the study if the subject's safety or wellbeing is compromised by his or her further participation in the study. Concern for the interests of the subject must always prevail over the interests of the study.

4.3.3 Procedures for Handling Withdrawals

If a subject is withdrawn from the study, attempts will be made to complete and document the follow-up assessments. If the subject is withdrawn from the study after receiving IP, every effort will be made to ensure that the relevant safety assessments are completed. The subject may also be asked by the investigator to complete other study assessments.

If the subject withdraws from the study and also withdraws consent for disclosure of future information, CSL may retain and continue to use any data collected before such withdrawal of consent.

4.3.4 Subjects Lost to Follow-up

Not applicable.

4.3.5 Replacement Policy

The decision to replace subjects will be at the discretion of CSL.

5 Study Interventions

All subjects will receive standard of care according to the study site's normal clinical practice at all times during the study. No standard of care practices will be interrupted or forgone as a result of enrollment evaluation, IP infusion, or other aspects of the study.

5.1 Investigational Products

The IPs in this study are BE1116 and placebo.

5.1.1 Description of BE1116

Details of BE1116 are provided in Table 2.

The lyophilized powder of BE1116 will be provided in labeled, single-use, glass vials. The product is provided in a study co-packaged kit (IP study kit) containing 3 vials of BE1116 (or placebo), 3 vials of sterile water for injection, and 3 Mix2Vial™ devices. The lyophilized concentrate of BE1116 must be reconstituted with sterile water for injection.

The formulation of BE1116 to be used in this clinical study is unchanged from the commercial form and will be labeled as IP.

Dose administration information is included in Section 5.1.3.1.

Table 2 Description of BE1116

Substance name	BE1116
Trade name	Kcentra® / Beriplex®
Active substance	Concentrate of human coagulation Factors II, VII, IX, and X (PCCs), Protein C, and Protein S
Excipients	Heparin, antithrombin III, human albumin, sodium chloride, sodium citrate, hydrogen chloride, sodium hydroxide
Dosage form	Powder for reconstitution (1000 IU/vial) Provided together with diluent (sterile water for injection)
Dose	• 2000 IU for subjects with body weight < 75 kg (< 165 lbs) (2 vials) • 3000 IU for subjects with body weight ≥ 75 kg (≥ 165 lbs) (3 vials) (Weight may be estimated and / or measured.)
Dosing regimen	Single dose
Infusion volume	Based upon dose: • 80 mL for 2000 IU (2 vials) • 120 mL for 3000 IU (3 vials)
Mode of administration	Intravenous infusion [a]

IP = investigational product; PCC = prothrombin complex concentrate.

[a] Further details regarding dose administration are provided in the Site IP Manual.

BE1116 will be manufactured by CSL in accordance with ICH Good Manufacturing Practice (GMP) guidelines and local regulatory requirements.

5.1.2 Description of Placebo

Details of placebo are provided in Table 3. Placebo is a sterile filtered preparation comprising the BE1116 buffer and human albumin to support lyophilization cake formation. Placebo vials will match BE1116 vials in appearance. The lyophilized concentrate of placebo must be reconstituted with sterile water for injection.

After reconstitution, each vial contains 2 to 4 mg/mL human albumin in sterile water for injection at a target pH of 6.5 to 7.5. The amount of albumin in the reconstituted placebo is the same as in the reconstituted drug product, BE1116. The placebo contains the same amounts of the excipients sodium chloride and sodium citrate as used for the drug product BE1116.

Details of packaging and administration are the same as for BE1116. Dose administration information is included in Section 5.1.3.1.

Table 3 Description of Placebo

Substance name	Not applicable
Substance	Buffer solution with human albumin without active ingredient and without proteins and impurities related to the active ingredient or antithrombin III and heparin
Trade name	Not applicable
Dosage form	Powder for reconstitution (same vial as 1000 IU/vial for BE1116) Provided together with diluent (sterile water for injection)
Dose	• 2 vials for subjects with body weight < 75 kg (< 165 lbs) • 3 vials for subjects with body weight ≥ 75 kg (≥ 165 lbs) (Weight may be estimated and / or measured.)
Dosing regimen	Single dose
Infusion volume	Based upon dose: • 80 mL for 2 vials • 120 mL for 3 vials
Mode of administration	Intravenous infusion [a]

IP = investigational product.

[a] Further details regarding dose administration are provided in the Site IP Manual. Preparation and administration of placebo will be identical to BE1116. The placebo presentation looks the same as BE1116, and the kit contains the same vials and accessories as in the kit containing BE1116.

Placebo will be manufactured by CSL in accordance with ICH GMP guidelines and local regulatory requirements.

5.1.3 Dosing and Administration of Investigational Products

5.1.3.1 Dose Administration

Subjects who were enrolled but subsequently discovered to have an exclusion criterion prior to IP administration should not be administered IP.

Each subject will receive a single dose of either BE1116 or placebo, according to their randomization (see Section 6). Enrolled subjects will receive IP from blinded study IP kits.

A fixed dose (number of vials) will be administered according to the subject's body weight (estimated or measured) (see Sections 5.1.1 and 5.1.2).

The start of the IP infusion must be within 90 minutes after arrival at the hospital.

Details of dose administration, including the start and stop times of the infusion and any infusion interruptions, will be recorded in the eCRF if available.

The investigator (or other applicable site staff) will administer or dispense IP only to subjects included in this study following the procedures set out in this study protocol.

Detailed information on the preparation and administration of IP is provided in the Site IP Manual.

5.1.3.2 Dosing Modification

A partial dose of IP may be administered (eg, if there is a product error or user error when reconstituting / administering the IP if the remainder of the IP is unaffected, when infusion needs to be stopped due to patient care issues, or if vial(s) are damaged).

5.1.3.3 Treatment Compliance

All doses of BE1116 (or matching placebo) will be administered by the investigator (or other applicable site staff) at the study site, and details will be recorded in the eCRF.

5.1.3.4 Overdose

Overdose of BE1116 is defined as the infusion of more than the protocol-specified dose. The effects of any potential overdose with BE1116 have not been studied. In case of overdose, the subject should be closely monitored, and supportive treatment should be administered, as needed.

See Section 9.6.5 for overdose reporting requirements.

5.1.4 Description of Investigational Medical Device Constituent

Each IP study kit will include 3 Mix2Vial™ devices, as described in Section 5.1.1.

5.1.5 Packaging, Labeling, Supply, and Storage

5.1.5.1 Packaging and Labeling

The IP will be packaged and labeled according to current ICH GMP and GCP guidelines, and national legal requirements. Specific details regarding the packaging of IP are provided in the Site IP Manual.

5.1.5.2 Supply and Storage

Study kits containing IP will be supplied to the study sites by CSL or delegate.

The kits must be stored under temperature-controlled and monitored conditions in a secure storage area, and must not be frozen, as specified in the Site IP Manual.

Blinded, sealed IP study kits containing either BE1116 or placebo will be maintained in the trauma bay, or a location where they are readily accessible, at the study site at all times during the study. See also Section 6.1.

Reconstitution of the vials should be performed at the time of dosing; therefore, there should be no storage of reconstituted vials.

If an IP study kit is opened for a subject, it should not be used for any other subject, even if the kit is not subsequently used.

5.1.6 Access to Investigational Product After the End of Study

Subjects will not be provided with BE1116 by CSL after completion or discontinuation from the study.

5.2 Accountability and Destruction

The IP must be used only as directed in the clinical study protocol.

The investigator or delegate will confirm receipt of all shipments of IP in the interactive response technology (IRT) system.

All supplies of IP must be accounted for throughout the study. IP accountability should be performed in the IRT system when feasible within 24 hours after randomization.

Records for the delivery of IP to the study site, the inventory at the study site, the use by each subject, and the destruction or return of IP to CSL or designee must be maintained by the study site personnel delegated by the investigator using the appropriate form or IRT system.

The study site personnel delegated by the investigator must provide reasons for any discrepancies in drug accountability in the IRT system.

Further details regarding accountability and destruction of IP are provided in the Site IP Manual.

5.3 Other Interventions

The IP will be administered in addition to the study site's standard resuscitation methods and protocol.

6 Allocation to Treatment

6.1 Subject Assignment

Eligible subjects will be assigned an IP study kit with the next available sequential subject number, as described in Section 6.2. The subject identification number will be used to identify the subject for the duration of the study. Subject identification numbers will not be reassigned or reused.

6.2 Randomization Procedures

The IRT external service provider will prepare the study randomization code according to the approved specifications.

Subjects will be randomized in a 1:1 ratio to either the BE1116 or placebo treatment arm. Randomization will be stratified by study site.

The blinded study staff will use the IRT system to randomize subject placeholders, resulting in a unique subject number assignment and pre-assignment of an IP study kit prior to subject arrival at the hospital. The research pharmacy staff (or equivalent) will record the IRT-assigned unique subject number on the label of the applicable kit and send the kit to be stored in the trauma bay, or a location where it is readily accessible. Once a subject meets all the eligibility criteria, the trauma team (or other applicable site staff) will select and open the IP study kit with the next available sequential subject number, and the subject will be considered randomized (enrolled). The date and time of opening the IP study kit (randomization) will be recorded.

6.3 Blinding Procedures

Additional details on unblinding are provided in the study blinding plan.

6.3.1 Blinding Method

CSL (or designee) will provide blinded IP study kits to the study sites. The IP will be packaged and labeled to ensure blinding is maintained.

Investigational site staff, including the investigators, physicians, nurses, and pharmacists, will be blinded to treatment allocation. Subjects will also be blinded to treatment allocation (double-blind).

CSL personnel (or delegates) will be blinded to treatment allocation, except for those personnel involved in the IRT system and clinical trial supply who will be unblinded.

A separate statistician and programming team will provide unblinded data to the IDMC for adequate safety and efficacy reviews as planned. All individuals involved will be placed under strict confidentiality to protect the integrity of the study. If the IDMC makes a recommendation to stop the study, a few designated senior Sponsor stakeholders will access

the unblinded data before endorsing the recommendation. These senior stakeholders will not participate in any study conduct or analyses after unblinding.

Review of unblinded data by treatment arms will occur during the scheduled interim analyses, the final analysis, and for IDMC reviews. In addition, individual subjects may be unblinded during the study in emergency situations for reasons of subject safety, if knowing treatment assignment will change medical management.

6.3.2 Breaking the Blind for an Emergency

The randomization code for individual subjects may be unblinded to a study site during the study in emergency situations for reasons of subject safety, if knowing treatment assignment will change subject management. In case of an emergency situation for the reason of subject safety, the investigator should use the IRT system to identify the treatment allocation for a subject. Whenever possible, the investigator should consult with CSL before unblinding the randomization code. The reason for unblinding the randomization code must be fully recorded in the subject's source documents, and the investigator must follow the defined procedures provided in the study reference manuals. The subject's treatment allocation should not be recorded in the subject's source document.

6.3.3 Planned Unblinding Procedures

Periodic data reviews will be performed by the IDMC (see Section 3.8.1). With authorization by CSL, randomization codes will be provided to the unblinded statistician (external service provider) performing analyses for the interim analyses and / or IDMC, via the CSL Central Data Warehouse.

At the end of the study, CSL will authorize that the study be unblinded after database lock. The randomization codes will be accessed via the CSL Central Data Warehouse.

6.3.4 Ad-hoc Safety Unblinding

CSL's Global Clinical Safety and Pharmacovigilance personnel may, on an ad-hoc basis, unblind the randomization code directly in the IRT at any time during the study, because of a safety concern. The purpose of the unblinded data review is to determine if there is a risk to subject safety that would require further action either for the individual management of a study subject or for the ongoing conduct of the study. The need to unblind a subject or group of subjects may not necessarily arise because of an SAE. The need to unblind on an ad-hoc

basis will be determined by CSL's Global Clinical Safety and Pharmacovigilance senior leadership.

7 Contraindications, Permitted Therapies, and Prohibited Therapies

7.1 Contraindications

BE1116 is contraindicated in the following:

- Subjects with known anaphylactic or severe systemic reactions to BE1116 or any components in BE1116 including heparin, FII, FVII, FIX, FX, Proteins C and S, antithrombin III, and human albumin
- Subjects with disseminated intravascular coagulation
- Subjects with known heparin-induced thrombocytopenia; BE1116 contains heparin

7.2 Permitted Therapies

Any medication or therapy determined by the treating trauma team to be required by the subject is allowed following IP administration, with the exception of PCCs, activated PCC, and FVIIa (see Section 7.3).

7.3 Prohibited Therapies

Subjects will be excluded from the study if they have received a known anticoagulation treatment within the past 3 months.

Prohibited medications during the study are summarized in Table 4.

Table 4 Summary of Prohibited Medications

Medication	Dose	Prohibited Period of Use
3F-PCC	Any	From trauma time through 6 hours after randomization
4F-PCC	Any	From trauma time through 6 hours after randomization
aPCC (FEIBA)	Any	From trauma time through 6 hours after randomization
Factor VIIa	Any	From trauma time through 6 hours after randomization

3F-PCC = 3-factor prothrombin complex concentrate; 4F-PCC = 4-factor prothrombin complex concentrate; aPCC = activated prothrombin complex concentrate; FEIBA = Factor VIII inhibitor bypassing activity; IP = investigational product.

7.4 Lifestyle Restrictions

Not applicable.

8 Study Procedures and Visit Schedule

8.1 Clinical Procedures

The timing and frequency of the clinical procedures described in the following sections are detailed in the Schedule of Assessments. More frequent assessments may be performed, if clinically indicated, at the discretion of the investigator.

The date and time of arrival at the hospital will be recorded in the eCRF. This will be considered the start of hospitalization.

Where possible / applicable, the dates and times of study assessments will be recorded in the eCRF.

8.1.1 Demographics and Clinical Conditions

Subject demographics and clinical conditions to be recorded in the eCRF are summarized in Table 5.

The clinical laboratory tests (hematology, coagulation, and arterial or venous blood gases) will be performed at local laboratories per local standard of care. Results should be retained

at the study site as source data. The initial hematology, coagulation, and blood gas measurements only will be recorded in the eCRF from medical records.

Table 5 Demographics and Clinical Conditions

Assessment	Description
Vital signs, body weight, and height [a]	• Weight (kg) (estimated or measured on arrival at hospital; if estimated, weight may also be subsequently measured) • Height (cm) (measured or taken from medical history) • Supine systolic and diastolic blood pressure (mmHg) • Pulse rate (bpm) • Respiratory rate (breaths per minute) • Pulse oximetry (%) • Body temperature (°C)
Glasgow Coma Scale [b]	• Record individual components if available, otherwise total score. • See Appendix 3
RABT score (if applicable) [b]	• See Table 1
Demographics [c]	• Sex, race, ethnicity, and other factors according to the eCRF and regulatory and local requirements. Either actual age or estimated age will be collected during Screening. The actual age of subjects will be recorded, once confirmed. An enrolled subject whose confirmed age does not meet the inclusion criteria must be reported to Sponsor and the IRB / IEC as a prompt reporting event.
Medical history and Charlson Comorbidity Index [c]	• Medical history includes all bleeding and coagulation history and surgical conditions, and any other pertinent findings related to the Charlson Comorbidity Index, which will be recorded (see Appendix 6)
Prior and concomitant medications [c]	• Medications that impact bleeding and coagulation (including antiplatelets) for approximately 1 week prior to randomization will be recorded when feasible • Tranexamic acid (if administered) • Prohibited concomitant medications from trauma time through 6 hours after randomization • Anticoagulants, thrombolytic agents, and procoagulants used to treat AESIs • In-hospital low-dose prophylactic anticoagulants are not considered concomitant medications
Concomitant procedures	• Any surgical or interventional radiological procedures, or other life-saving interventions, used to treat an SAE or AESI at any time through the study will be recorded as a concomitant procedure.
Hematology [d]	• Hemoglobin • Hematocrit • Platelets

Assessment	Description
Coagulation [d]	• International normalized ratio and / or prothrombin time
Arterial or venous blood gases [d]	• If reported by clinical laboratory: Base excess • If base excess not reported by clinical laboratory, then the study site will collect the following parameters so that base excess can be calculated: ○ pH ○ pCO_2 ○ pO_2 ○ HCO_3
Mode of transport [e]	• Mode of transport to the hospital will be recorded, eg, ground (ambulance), air (medical flight), and / or self-presenter (walk-in or vehicle)
Life-saving interventions [e]	• Any prehospital life-saving interventions and any life-saving interventions performed on arrival at the hospital (eg, tracheal intubation, tourniquet, thoracotomy, etc.)
Mechanism of injury [e]	• Mechanism of injury (blunt, penetrating, or both)
Date and time of call to emergency services and arrival at trauma scene [e]	• Date and time of call to emergency services (if available) • Date and time of arrival of emergency medical services at trauma scene (if available)
Hospital arrival time and hospital admission time [e]	• Hospital arrival time (should be recorded per study site processes; hospital arrival time will determine timing of IP administration) • Hospital admission time (should be recorded per study site processes)
Injury Severity Score [f]	• Scoring relating to the injury(ies) sustained from the trauma (Appendix 4). The Injury Severity Score may be calculated after study completion.

AESI = adverse event of special interest; eCRF = electronic case report form; IEC = Independent Ethics Committee; IRB = Institutional Review Board; RABT = Revised Assessment of Bleeding and Transfusion

[a] Vital signs obtained as part of standard of care will be recorded at Screening prior to infusion, except as described. These include supine systolic and diastolic blood pressure (mmHg), pulse rate (bpm), respiratory rate (breaths per min), pulse oximetry (%), and body temperature (°C). Body weight (kg) will be estimated or measured on arrival at the hospital and used to define the dose of IP. If estimated, weight may also be subsequently measured. Height (cm) will be measured or taken from medical history.

[b] To be performed at Screening prior to IP infusion, except as indicated.

[c] To be recorded when feasible.

[d] To be recorded from the subject's medical records (if available). The initial hematology, coagulation, and blood gas measurements only will be recorded in the eCRF from medical records. Initial = the first value obtained after arrival at the hospital prior to IP infusion.

[e] To be recorded at any time from Screening through the In-hospital Follow-up Period from the subject's medical records.

[f] To be recorded at any time during the In-hospital Follow-up Period from the subject's medical records.

8.1.2 Efficacy Assessments

All efficacy data will be recorded in the eCRF from the subject's medical records.

8.1.2.1 Survival Status

The survival status of the subject during primary hospitalization will be recorded from randomization up to the time of death, hospital discharge, or Day 30, whichever occurs first. The date and time of death / hospital discharge / Day 30 will be recorded, as applicable. The survival status check during primary hospitalization will be at 24 hours (the date and time of death / hospital discharge will be recorded, as applicable). If subject is discharged alive prior to 6 hours, then the subject will be followed up to assess 6-hour survival status, SAEs, and AESIs.

The primary cause of death, as determined by the investigator, will be recorded.

Discharge / transfer information will be recorded (eg, transferred to another hospital, transferred to skilled nursing facility, transferred to in-patient rehabilitation, discharged to home, or transitioned to comfort care / palliative care). If subject is discharged within 2 days of enrollment, discharge time will also be recorded. Additionally, if the subject is designated "do not resuscitate", the date and time (where applicable) will be recorded.

8.1.2.2 Surgical or Interventional Radiological Procedures Performed to Stop Bleeding Related to the Primary Injury, Through the First 24 Hours After Randomization

All surgical or interventional radiological procedures performed to stop bleeding related to the primary injury, through the first 24 hours after randomization, will be recorded.

8.1.2.3 Blood Product Transfusion up to 24 Hours

Transfusion of blood products (time and quantity) before arrival at the hospital through the first 24 hours after randomization (RBCs, FFP, whole blood, cryoprecipitate, intraoperative salvaged [cell-saver] blood, and platelets) will be recorded according to the period in which the blood component transfusion started: before arrival at the hospital; from arrival at the hospital to the time of randomization; from randomization to 6 hours after randomization; and from 6 to 24 hours after randomization (see Section 8.4).

Administration of IV fluids (crystalloids and / or colloids) will also be recorded for the same time periods.

8.1.3 Safety Assessments

Safety assessments are summarized in Table 6. The investigator should make an evaluation of all available safety assessment results with respect to clinically relevant abnormalities.

Table 6 Safety Assessments

Assessment	Description
SAEs [a]	• SAEs will be recorded; see Section 9 for further details
AESIs [a]	• AESIs will be recorded; see Section 9 for further details (AESIs are defined in Section 9.1.3)
Pregnancy status [b]	• Pregnancy status (positive / negative) • Pregnancies in female subjects will also be recorded; see Section 9.6.6 for further details
ICU assessments [c]	• ARDS, multiple organ failure, and AKI requiring renal replacement therapy (see Section 9.1.3)

AESI = adverse event of special interest; AKI = acute kidney injury; ARDS = acute respiratory distress syndrome; eCRF = electronic case report form; ICU = intensive care unit; SAE = serious adverse event

[a] To be recorded from the time of randomization through the In-hospital Follow-up Period until death / hospital discharge / or Day 30, whichever occurs first. If subject is discharged alive prior to 6 hours, then the subject will be followed up to assess 6-hour survival status, SAEs, and AESIs.

[b] To be recorded from the subject's medical records (if available).

[c] To be recorded daily when a subject is in the ICU. ICU assessments will be collected from the medical record of the subject using data collected as part of standard of care.

8.1.4 Other Assessments

8.1.4.1 Medical Resource Utilization

Medical resource utilization during primary hospitalization, up to the time of death, hospital discharge, or Day 30, whichever occurs first, will be assessed through the following data recorded in the eCRF:

- Start and stop dates and times of ventilator use (to calculate days with ventilator use)
- Start and stop dates and times in ICU (to calculate ICU days)
- Start and stop dates of primary hospitalization (to calculate hospital length of stay)

The assessments above will be analyzed overall and separately as subgroups for those who die during primary hospitalization and those who remain alive during primary hospitalization.

8.2 Blood Samples

It is not planned to collect any blood samples as part of the study; clinical laboratory safety tests, as described in Section 8.1.1, will be recorded from the subject's medical records.

Components of the Denver postinjury multiple organ failure score, KDIGO AKI, and Berlin Criteria for ARDS will be collected from medical records, if available, even if all components are not collected per standard of care (Section 9.1.3).

8.3 Retention of Samples

Not applicable.

8.4 Prior and Concomitant Therapies

Medications that impact bleeding and coagulation (including antiplatelets) for at least 1 week prior to randomization will be recorded when feasible in the Concomitant and Prior Medications eCRF. In-hospital low-dose prophylactic anticoagulants are not considered concomitant medications.

Other medications to be recorded on the eCRF are as follows:

- Tranexamic acid (if administered)
- Blood product transfusions and IV fluids administration before arrival at the hospital through the first 24 hours after randomization
- Prohibited concomitant therapies taken from trauma time through 6 hours after randomization (see Section 7.3)
- Anticoagulants, thrombolytic agents, and procoagulants used to treat AESIs at any time through the study

Any surgical or interventional radiological procedures, or other life-saving interventions, that are used to treat an SAE or AESI at any time through the study will be recorded as a concomitant procedure.

Surgical or interventional radiological procedures performed to stop bleeding related to the primary injury, through the first 24 hours after randomization, are described in Section 8.1.2.2.

8.5 Visit Schedule

8.5.1 Assessment Time Windows

The timing and frequency of the study assessments are described in the Schedule of Assessments. Time windows are summarized in Table 7.

Table 7 Time Windows for Assessments

Study Period	Time Window
Screening and Randomization (Enrollment)	Subjects must be screened and randomized within 90 minutes after hospital arrival and before the start of IP infusion
Treatment Period (Start of IP infusion through completion of IP infusion)	IP infusion must be started post-randomization and within 90 minutes after hospital arrival
In-hospital Follow-up Period	Subjects will be followed up until death, discharge from hospital, or Day 30, whichever occurs first. If subject is discharged alive prior to 6 hours, then the subject will be followed up to assess 6-hour survival status, SAEs, and AESIs.

IP = investigational product.

8.5.2 Screening and Randomization (Enrollment) Period

Screening will begin once the subject has arrived at the hospital (eg, emergency department, trauma bay, or operating room). Upon arrival, subjects will be assessed for eligibility. For details regarding Informed Consent, refer to Section 12.3 and Section 12.3.1.

The following Screening assessments will be performed and recorded:

- Vital signs (supine systolic and diastolic blood pressure, pulse rate, respiratory rate, pulse oximetry, and body temperature)
- Body weight (estimated or measured; if estimated, weight may also be subsequently measured)
- Height (measured or taken from medical history)
- Glasgow Coma Scale (record individual components if available, otherwise total score)
- RABT score (if applicable)

- Hematology, coagulation, and arterial or venous blood gases (initial measurements only to be recorded; initial = first value obtained after arrival at the hospital prior to IP infusion)
- Inclusion / exclusion criteria check

Once a subject meets all the eligibility criteria, the trauma team (or other applicable site staff) will select and open the IP study kit with the next available sequential subject number, and the subject will be considered randomized (enrolled).

If study sites have sufficient safeguards and processes in place, more than 1 subject who meets the eligibility criteria may be randomized (enrolled) in the study at the same time, assigned IP, and treated.

8.5.3 Treatment Period

The start time of the IP infusion will be within 90 minutes after arrival at the hospital. The blinded, sealed IP study kits will be available to the trauma team (see Section 6.2). At the time of subject randomization (enrollment), the selected kit will be provided to the trauma team (or other applicable site staff) for IP reconstitution and administration.

- IP administration: must start within 90 minutes after arrival at the hospital (eg, emergency department, trauma bay, or operating room) (see Section 5.1.3.1)

IP administration is in addition to the site's standard resuscitation methods and protocol.

8.5.4 In-hospital Follow-up Period

Subjects will be followed up until death, discharge from hospital, or Day 30, whichever occurs first. If subject is discharged alive prior to 6 hours, then the subject will be followed up to assess 6-hour survival status, SAEs, and AESIs. Transfer to another healthcare facility will be considered as discharge from hospital. For details regarding Informed Consent, refer to Section 12.3 and Section 12.3.1.

The following assessments will be performed:

- IP accountability (to be performed in the IRT system when feasible within 24 hours after randomization)
- Demographics (to be recorded when feasible)*
- Medical history and Charlson Comorbidity Index (to be recorded when feasible)*

- Prior and concomitant medications (medications that impact bleeding and coagulation [including antiplatelets] for at least 1 week prior to randomization; tranexamic acid [if administered]; prohibited concomitant medications administered from trauma time through 6 hours after randomization; and anticoagulants, thrombolytic agents, and procoagulants used to treat AESIs; to be recorded when feasible)*
- Concomitant procedures (any surgical or interventional radiological procedures, or other life-saving interventions, used to treat an SAE or AESI at any time through the study will be recorded)*
- SAEs and AESIs
- Survival status (survival status of the subject during primary hospitalization will be recorded from randomization up to the time of death, hospital discharge, or Day 30, whichever occurs first. The date and time of death / hospital discharge / Day 30 will be recorded, as applicable. For expired subjects, details of their death may be recorded on the Subject Death Record. The survival status check during primary hospitalization will be at 24 hours [the date and time of death / hospital discharge will be recorded, as applicable]. If subject is discharged alive prior to 6 hours, then the subject will be followed up to assess 6-hour survival status, SAEs, and AESIs)*
- Blood product transfusions (eg, RBCs, FFP, whole blood, cryoprecipitate, intraoperative salvaged [cell-saver] blood, and platelets) and IV fluid administrations (crystalloids and / or colloids) before arrival at the hospital through the 24 hours after randomization*
- All surgical or interventional radiological procedures performed to stop bleeding related to the primary injury, through the first 24 hours after randomization*
- Mode of transport to the hospital*
- Life-saving interventions (prehospital and on arrival at hospital)*
- Mechanism of injury (blunt, penetrating, or both)*
- Date and time of call to emergency services (if available)*
- Date and time of arrival of emergency medical services at trauma scene (if available)*
- Hospital arrival time (should be recorded per study site processes; hospital arrival time will determine timing of IP administration)*
- Hospital admission time (should be recorded per study site processes)*
- Injury Severity Score (may be calculated after study completion)*
- Pregnancy status (pregnancies will also be reported as described in Section 9.6.6)*

- Daily assessments for ARDS, multiple organ failure, and AKI requiring renal replacement therapy recorded when a subject is in the ICU. ICU assessments will be collected from the medical record of the subject using data collected as part of standard of care*
- Medical resource utilization (see Section 8.1.4.1)*
- Discharge / transfer location*
- Date and time if subject is designated "do not resuscitate"*

*Recorded from medical records (as applicable).

If subject is discharged within 2 days of enrollment, discharge time will also be recorded.

8.5.5 Withdrawal Assessments

If a subject is withdrawn from the study, the investigator should make every effort to complete and document the follow-up assessments, as described in Section 8.5.4.

9 Adverse Events

Nonserious AEs (except AESIs) will not be recorded in this study. However, information regarding AEs is provided below, to be used in the context of assessing AESIs and SAEs, which will be recorded in this study.

9.1 Definitions

9.1.1 Adverse Event

As per the ICH Topic E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting), an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal, clinically significant laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

The primary safety risk factors identified for this study population are:

- In-hospital SAEs with a fatal outcome up to 30 days after the start of IP infusion
- In-hospital TEEs up to 30 days after the start of IP infusion

9.1.2 Serious Adverse Event

In this study, a SAE is defined as any untoward medical occurrence that at any dose meets at least one of the following criteria:

- **Results in death –** The event must be the cause of death for the SAE to meet this serious criterion. Refer to Section 9.6.3 for details regarding reportability.
- **Is life-threatening** – The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it had been more severe.
- **Requires in-patient hospitalization or prolongation of existing hospitalization** – CSL considers "hospitalization or prolongation of existing hospitalization" for at least 24 hours as the defining criterion for an SAE. Hospital admissions for planned surgery or for normal disease management procedures (eg, chemotherapy) are not considered as defining criteria for SAEs.
- **Results in persistent or significant disability or incapacity.**
- **Is a congenital anomaly or birth defect.**
- **Is medically significant** – A medically significant event is defined as an event that does not necessarily meet any of the SAE criteria, but which is judged by a physician to potentially jeopardize the subject or require medical or surgical intervention to prevent one of the above outcomes listed as an SAE criterion.

Adverse events that do not fall into the above categories are defined as nonserious AEs.

A preexisting medical condition should be recorded as an SAE only if the frequency, severity, or character of the condition worsens during the study. A preexisting medical condition is one that is present at the time of randomization.

9.1.3 Adverse Events of Special Interest

The AESIs in this study are:

- TEEs, symptomatic or asymptomatic, and arterial or venous (eg, deep vein thrombosis, pulmonary embolism, ischemic stroke [including thromboembolic stroke], and myocardial infarction)
- ARDS

- Multiple organ failure
- AKI requiring renal replacement therapy (dialysis, hemofiltration, or hemodiafiltration)

Note: superficial thromboses will not be included as AESIs

Multiple Organ Failure

Multiple organ failure will be assessed using the Denver score [Sauaia et al, 2009] (see Appendix 5). Components of the Denver postinjury multiple organ failure score will be collected from medical records, if available, even if all components are not collected per standard of care. The Denver score will be recorded in the eCRF in addition to the severity assessment described in Section 9.2.

Acute Kidney Injury

The definition of AKI follows the Kidney Disease Improving Global Outcomes (KDIGO) guidelines [Kidney International, 2012].

AKI is defined as any of the following:

- Increase in serum creatinine by ≥ 0.3 mg/dL (≥ 26.5 µmol/L) within 48 hours; or
- Increase in serum creatinine to ≥ 1.5 × baseline, which is known or presumed to have occurred within the prior 7 days; or
- Urine volume < 0.5 mL/kg/h for 6 hours.

Components of the KDIGO AKI will be collected from medical records, if available, even if all components are not collected per standard of care. The reporting requirements for AESIs are described in Section 9.6.2.

Acute Respiratory Distress Syndrome

ARDS will be assessed using the Berlin criteria [ARDS Definition Task Force, 2012; Fan et al, 2018; Matthay et al, 2021] (Appendix 7). Components of the Berlin Criteria for ARDS will be collected from medical records, if available, even if all components are not collected per standard of care.

9.2 Severity of Adverse Events

The severity of each AESI and SAE is to be assessed by the investigator as follows:

Severity	Definition
Mild	A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Severe	A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

CDISC SDTM Severity Intensity Scale for Adverse Event Terminology.

9.3 Causality of Adverse Events

The causal relationship of an AESI or SAE to IP **must always be assessed** by the investigator. All AESIs and SAEs will be classified as either **related** or **not related** to IP. If a causality assessment is not provided for an AESI or SAE, that event will be considered as related to the IP.

The degree of certainty with which an AESI or SAE is attributed to IP or an alternative cause (eg, natural history of the underlying disease, concomitant therapy) will be determined by how well the event can be understood in terms of:

- Known pharmacology of IP.
- Clinically and / or pathophysiologically plausible context.
- Reaction of a similar nature previously observed with similar products, or reported in the literature for similar products as being product related (eg, headache, facial flushing, pallor).
- Plausibility supported by the temporal relationship (eg, the event being related by time to administration or termination of treatment with IP, or drug withdrawal).

9.4 Observation Period for Adverse Events

The observation period for the reporting of AESIs and SAEs for an individual subject will start at the time of randomization and finish with the end of the In-hospital Follow-up Period (ie, up to the time of death / hospital discharge / Day 30, whichever occurs first; if subject is

discharged alive prior to 6 hours, then the subject will be followed up to assess 6-hour survival status, SAEs, and AESIs).

If the investigator becomes aware of an SAE that has started after the observation period has finished, and there is at least a possible causal relationship with the IP, the event must be reported to CSL (see Section 9.6.3).

9.5 Follow-up of Adverse Events

Every effort should be made to follow AESIs and SAEs until resolution or stabilization. Ongoing AESIs and SAEs that have not resolved or stabilized will be followed until the subject completes the study.

9.6 Adverse Event Reporting

9.6.1 Adverse Events

Nonserious AEs (except AESIs) will not be recorded in this study.

9.6.2 Adverse Events of Special Interest

AESIs are defined in Section 9.1.3. Any AESI should be reported following expedited reporting procedures, as described for SAEs (Section 9.6.3). Any surgical or interventional radiological procedures, or other life-saving interventions used to treat SAEs or AESIs and the use of therapeutic anticoagulants, thrombolytic agents, or procoagulants to treat AESIs will be reported.

AESIs, even those with a fatal outcome, should still be reported as AESIs. If an AESI meets the definition of an SAE (Section 9.1.2), then the AESI should be marked as meeting serious criteria on the electronic data capture system.

9.6.3 Serious Adverse Events

This study will comply with all applicable regulatory requirements and adhere to the full requirements of ICH Topic E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

For SAEs occurring during the study, the investigator or delegate will enter all relevant information in the eCRF.

SAEs that occur during the course of the study, whether or not causally related to the IP, must be entered into the eCRF immediately (within 24 hours of the investigator becoming aware of the event).

Any SAE that occurs after the observation period has finished and is considered to be causally related to the IP must be **reported immediately (ie, within 24 hours of the investigator becoming aware of the event) to CSL.** Such events are not entered into the eCRF and should be reported on the Serious Adverse Event Data Collection Form (paper) and sent to CSL Global Clinical Safety and Pharmacovigilance and will be documented in the CSL safety database only.

The minimum reporting requirements for reporting of SAEs include:

- Subject identification number
- Suspected medicinal product and / or procedure
- Event term
- Reporting source identification

If the minimum requirements for reporting are fulfilled, the investigator should not wait to receive additional information to fully document the event.

In addition, the investigator must:

- Report relevant SAEs as required to the relevant IRB / IEC within the timeframe specified by the IRB / IEC. Refer to Section 9.7.
- If the subject is an active participant in the study:
    - Enter follow-up information in the eCRF until the SAE has resolved, or, in the case of permanent impairment, until stabilized
    - Ensure that the causality assessment for all SAEs is entered in the eCRF
- If the subject is no longer participating in the study, report the follow-up information to CSL when available
- A SAE resulting in death up to the timeline for initial reporting (ie, within 24 hours of the investigator becoming aware of the event) does not require reporting as an SAE unless considered causally related to IP by the investigator.
- If a SAE / AESI is previously reported and subsequently results in death, the SAE / AESI outcome must be updated and reported.

9.6.4 Other Significant Events

Not applicable.

9.6.5 Overdose

Any overdose that is associated with an AESI or SAE will be recorded on an AE / SAE eCRF form (see also Section 9.6.3).

Details of overdose of IP (defined in Section 5.1.3.4) must be recorded in the study treatment administration eCRF.

9.6.6 Pregnancy

If a pregnant female subject is exposed to IP, CSL must be notified within 5 days of the investigator becoming aware and there should be entry of appropriate data into the eCRF. Pregnancy should be followed up as feasible to obtain the outcome of the pregnancy.

9.7 IRB / IEC Reporting Requirements

The time frame within which an IRB / IEC must be notified of deaths and IP-related unexpected SAEs is stipulated by each IRB / IEC. It is the investigator's responsibility to comply with the requirements for IRB / IEC notification. CSL will provide investigators with all details of all SAEs reported to health authorities.

10 Statistics

10.1 Sample Size Estimation

A sample size of 8000 subjects (4000 per treatment arm) is required to achieve 80% power while controlling for a one-sided type I error of 0.025 testing for superiority.

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10.2 Description of Study Populations

10.2.1 Intent-to-treat Population

The ITT Population will include all randomized subjects. In this population, analyses will be based on the treatment to which subjects were randomized, regardless of which treatment they actually received.

10.2.2 Modified Intent-to-treat Population

The Modified ITT (mITT) Population will include all subjects who receive a complete or partial dose of BE1116 or placebo. In this population, analyses will be based on the treatment to which subjects were randomized, regardless of which treatment they actually received.

10.2.3 Per-protocol Population

The Per-protocol (PP) Population will include all subjects in the ITT Population with no major protocol deviations that would potentially affect the assessment of the primary endpoint. Protocol deviations will be documented in the data review meeting held before the study data are unblinded.

10.2.4 Safety Population

The Safety Population will include all subjects in the ITT Population who receive a complete or partial dose of BE1116 or placebo, based on the treatment actually received.

10.3 Statistical Analyses and Methods

A complete description of the statistical analyses and methods will be available in the SAP.

10.3.1 Subject Disposition and Characteristics

10.3.1.1 Subject Disposition

The numbers of subjects who were randomized (enrolled), dosed, and who completed or withdrew from the treatment and / or study, were discharged or transferred, and died, will be presented in summary tables by treatment arm and total subjects. The reasons for discontinuing IP or withdrawing from the study will be listed by subject.

10.3.1.2 Subject Characteristics

Subject characteristics will be presented in summary tables. Continuous data will be summarized by descriptive statistics and categorical data will be summarized by frequency distributions. Age will be described as both a continuous and a discrete variable. Supportive data will be listed by subject. Clinical condition, including mechanism and type of injury, Injury Severity Score, Abbreviated Injury Scale (AIS) scores by region, Glasgow Coma Scale score, and RABT score will be summarized. Glasgow Coma Scale score will be summarized as a continuous variable and by categories ≤ 8, 9 to 12, and ≥ 13. RABT score will be summarized as a categorical variable. Charlson comorbidity index will be summarized as a continuous variable. Medical history (coded using the Medical Dictionary for Regulatory Activities) will be presented by system organ class and preferred term.

10.3.2 Efficacy Analyses

10.3.2.1 Primary Efficacy Endpoint Analyses

A Bayesian logistic regression will be used to compare all-cause mortality rate during the first 6 hours after randomization between the BE1116 and placebo arms, in the ITT Population.

Hypotheses:

Null Hypothesis (H_0): The all-cause 6-hour mortality rate in BE1116 is no better than control.

$$p_{kcentra} - p_{control} \geq 0$$

Alternative Hypothesis (H_1): The all-cause 6-hour mortality rate in BE1116 is lower than control.

$$p_{kcentra} - p_{control} < 0$$

Let y_i be the outcome of all-cause 6-hour death (1 = yes, 0 = no), the model is:

$$y_i \sim Bernoulli(p_i)$$

$$logit(p_i) = \beta_0 + \beta_1 treatment_i$$

where p_i is the probability of all-cause 6-hour mortality for subject i treatment intervention. The coefficient β_0 is the effect of placebo on the primary outcome in the logit scale. The

coefficient β_1 is the treatment effect of BE1116 over placebo on the primary outcome in the log OR scale. While this model gives direct estimates of ORs, the absolute risk differences (primary outcome of interest) will be derived using posterior draws from the coefficients. We assume independent normal prior distributions for the regression coefficients:

$$\beta_0 \sim Normal(\mu_0, \tau_0^2)$$

$$\beta_1 \sim Normal(\mu_1, \tau_1^2)$$

where, μs and τs are respectively the means and standard deviations of distributions.

For all interim and final analysis, the following noninformative priors are used: $\beta_0 \sim Normal(0, 10^2)$, $\beta_1 \sim Normal(0, 1^2)$. These priors are centered at zero, which for β_1 corresponds to a piori no intervention effect. This noninformative prior allows considerable uncertainty; the 95% interval for $\beta_1$on the OR scale ranges from 0.14 to 7.1 while avoiding unreasonable values.

The study will be considered a success and primary objective considered met if the posterior probability $Prob(p_{kcentra} - p_{control} < 0|\text{data})$ of lower all-cause 6-hour mortality in the BE1116 arm compared with the placebo arm is greater than the success threshold.

Interim analyses will occur when 1/4 (2000), 1/2 (4000), and 3/4 (6000) of the targeted 8000 subjects have data for the primary outcome. A group sequential approach will be utilized (see Section 10.3.4).

The success threshold for each applicable interim analysis and final analysis will be calibrated to protect overall type I error at 2.5% depending on the actual number of subjects with data on the primary outcome.

A nonbinding futility assessment at interim will also be considered. The study may stop for lack of benefit (futility) at interim if the posterior predictive probability of a lower all-cause 6-hour mortality for BE1116 compared with placebo upon trial completion is unlikely (< 8%) given the observed interim results. The futility boundary may be subject to change to reflect subsequent program-related decisions by CSL.

The posterior probability of lower all-cause 6-hour mortality in the BE1116 arm compared with the placebo arm will be reported. Posterior means and medians along with the relevant credible intervals will also be reported.

The study will continue to enroll 8000 subjects unless it is stopped for success or futility at one of the interim analyses.

Further details will be provided in the SAP.

10.3.2.2 Subgroup Analyses for Primary Endpoint

Subgroup analyses will be used to help determine whether the treatment effect for the primary endpoint is homogeneous across the study population. Each subgroup will be analyzed as for the primary analysis described in Section 10.3.2.1. Additional subgroup analyses may be detailed in the SAP.

The subgroups of interest for this study are as follows:

- Mechanism of trauma injury: any penetrating versus blunt
- Sex: male versus female
- Age: < 18 years versus 18 to 25 years versus 26 to 64 years versus > 64 years
- Weight-based dosing (2000 IU versus 3000 IU)
- Cause of death (hemorrhage versus non-hemorrhage).

Subgroup analysis of penetrating versus blunt trauma injury will provide evidence of BE1116 efficacy and safety in these populations with different mechanisms of traumatic injury. Blunt trauma, also called nonpenetrating trauma or blunt force trauma, is an injury to the body caused by forceful impact, injury, or physical attack with a dull object or surface. It is in contrast to penetrating trauma, in which an object pierces the body surface, causing an open wound [NIGMC, 2018].

Well documented subpopulation analysis of sex differences has shown that males experience an increased risk of mortality and hospital length of stay, and a higher incidence of complications, when compared with females [Liu et al, 2015].

Subgroup analysis of subjects aged < 18 years is important to confirm there are no important differences between older teenagers and young adults [Liras et al, 2016].

Subjects weighing between 50 and < 75 kg will receive 2000 IU and subjects weighing ≥ 75 kg will receive 3000 IU. This dosing regimen was designed to ensure equivalent doses of IP per kg body weight, so that all subjects receive equivalent blood concentrations of the coagulation factors present in the IP. This is the standard dosing used for non-trauma

subjects. However, it is possible that the total dose of IP, rather than the blood concentration of IP, will be most important in trauma patients with acute hemorrhage who are at risk of the lethal triad. This analysis will aim to determine whether total dose impacts outcomes.

10.3.2.3 Sensitivity Analyses for Primary Endpoint

A Bayesian logistic regression model, akin to the primary analysis model, but with site as a covariate together with an interaction term with treatment group will be used for other analyses of the primary endpoint. Further details will be provided in the SAP.

The primary analysis will be conducted as stated but adjusted for covariates together with an interaction term with treatment group in 4 separate analyses. Results for the primary endpoint in each analysis will be reported. The covariates will be as follows:

- Mechanism of injury: any penetrating versus blunt
- Sex: male versus female
- Age: < 18 years versus 18 to 25 years versus 26 to 64 years versus > 64 years
- Weight-based dosing (2000 IU versus 3000 IU)
- Cause of death (hemorrhage versus non-hemorrhage).

Additional sensitivity analyses might be defined in the SAP.

10.3.2.4 Supplementary Analyses for Primary Endpoint

Primary analysis based on the mITT and PP Population will also be conducted.

Other analyses may be specified in the SAP.

10.3.2.5 Secondary Efficacy Endpoint Analyses

All-cause in-hospital mortality up to hospital discharge or 24 hours after randomization (whichever occurs first) and all-cause in-hospital mortality up to hospital discharge or 30 days after randomization (whichever comes first), will be analyzed and summarized in the same manner as for the primary endpoint, ie, estimated by a Bayesian logistic regression model. The same noninformative priors as specified for the primary analysis will be used. In-hospital mortality will only be recorded and assessed for the primary hospitalization.

The difference in proportion of subjects who undergo surgical or interventional radiological procedures to stop bleeding related to the primary injury, up to 24 hours after randomization, will also be analyzed and summarized in a manner similar to the primary endpoint.

After the primary endpoint is deemed successful, the efficacy-related secondary endpoints will be analyzed sequentially in the order mentioned in Section 2.2.2. A gated testing approach will be used to account for multiplicity, and testing will proceed in a stepwise manner conditioned on observing a statistically significant result at each endpoint.

All secondary efficacy endpoints will be analyzed using the ITT, mITT, and PP Populations. Subgroup analysis will also be conducted similarly as for the primary endpoint.

Missing efficacy data handling is described in Section 10.3.2.7.

Further details will be specified in the SAP.

10.3.2.6 Exploratory Efficacy Endpoint Analyses

Summaries and analyses of exploratory endpoints described in Section 2.3 will be detailed in the SAP.

10.3.2.7 Missing Data

For efficacy endpoints, missing data will be handled according to the following rules.

- All-cause mortality up to 6 hours after randomization: if a subject withdrew from the study prior to 6 hours after randomization, the survival status at the time of study withdrawal will be carried forward to the 6-hour time point.
- All-cause in-hospital mortality up to 24 hours after randomization: if a subject withdrew or discharged from the study prior to 24 hours after randomization, the survival status at the time of study withdrawal or discharged will be carried forward to the 24-hour time point.
- All-cause in-hospital mortality up to 30 days after randomization: if a subject withdrew or discharged from the study prior to 30 days after randomization, the survival status at the time of study withdrawal or discharged will be carried forward to the 30-day time point.
- Use of surgical or interventional radiological procedures to stop bleeding: if a subject withdrew early or died, the usage of any surgical or interventional radiological procedures to stop bleeding up to the time of study withdrawal or death will be carried forward to the 24-hour time point.

Additional missing data will be handled as described in the SAP.

10.3.3 Safety Analyses

All endpoints related to safety analyses are secondary. The safety endpoints will be assessed using the Safety Population, unless otherwise noted.

The number and proportion of subjects with SAEs considered related to IP that occurred during primary hospitalization within the 30 days after randomization will be summarized by treatment arm.

All-cause in-hospital mortality will also be summarized.

The number and proportion of in-hospital overall and related TEEs up to 30 days after randomization will be summarized by treatment arm.

The incidence of the following AESIs will be summarized by treatment arm: ARDS; multiple organ failure; and AKI requiring renal replacement therapy.

Further details will be specified in the SAP.

10.3.4 Interim Analyses

The IDMC will meet to review unblinded data for both safety and efficacy according to the planned interim analysis schedule shown in Table 8.

The IDMC will have the flexibility to coordinate data reviews with the protocol-specified reviews as detailed below and ad-hoc reviews at the discretion of the IDMC Chair.

Table 8 Planned IDMC Reviews

IDMC Meeting Type	Number of Subjects Enrolled
Safety review	500
Safety review	1000
Scheduled Interim Analysis 1 – Safety and futility review	2000
Safety review	3000
Scheduled Interim Analysis 2 – Safety, efficacy, and futility review	4000
Safety review	5000
Scheduled Interim Analysis 3 – Safety, efficacy, and futility review	6000

IDMC = Independent Data Monitoring Committee

Commensurate with its mandate to review ongoing safety data, the IDMC will monitor unblinded deaths, AEs including SAEs and AESIs, as well as other safety data, with the objective of ensuring the safety of study participants.

Prior to a decision whether to recommend study termination for any reason, the IDMC will conduct a further data review of subgroups and other safety endpoints. The totality of the data, including the findings from all best available data at the time of the review, should be considered in deciding whether the overall benefit / risk is unfavorable enough to warrant a recommendation to terminate the study for safety concerns.

Interim Efficacy and Futility Analyses: Interim futility analyses will be conducted by the IDMC when approximately 25%, 50%, and 75% of subjects have been enrolled.

Stopping criteria for each interim analysis with 2000 (Interim Analysis 1), 4000 (Interim Analysis 2), and 6000 subjects (Interim Analysis 3) having data on the primary outcome respectively are displayed below.

The following success thresholds were considered:

The study will not stop for efficacy at Interim Analysis 1.

At Interim Analysis 2, the study will be assessed for overwhelming efficacy.

$P_{benefit}$: $Posterior\ Prob(p_{kcentra} - p_{control} < 0 | data_{interim}) > 99.8\%$

If the study does not stop at Interim Analysis 2, the study would continue and Interim Analysis 3 would be performed.

At Interim Analysis 3, the study will be assessed for overwhelming efficacy.

$P_{benefit}$: $Posterior\ Prob(p_{kcentra} - p_{control} < 0 | data_{interim}) > 99.3\%$

If the study does not stop at Interim Analysis 3, the study would continue and final analysis will be performed, and the primary objective is considered met if:

$P_{benefit}$: $Posterior\ Prob\left(p_{kcentra} - p_{control} < 0 | data_{final}\right) > 98.0\%$

The study will be considered to stop for futility (nonbinding) at each interim analysis if the posterior predictive probability of a lower all-cause 6-hour mortality for BE1116 compared with placebo upon trial completion is unlikely (< 8%) given results observed at interim.

P_{futile} : Prob$(Posterior\ Prob\left(p_{kcentra} - p_{control} < 0 | data_{final} > 98.0\%\right) | data_{interim}) < 8\%$.

An IDMC will be responsible for reviewing the interim results, and CSL will remain blinded unless the study is stopped. Further details on the safety and efficacy interim analyses and study conduct will be provided in the SAP and IDMC Charter. See also Section 3.8.1.

11 Quality Assurance

The study may be subject to an audit by CSL, an authorized representative(s) of CSL and / or inspections by an authorized health authority (eg, US FDA). Health authorities may request access to all study documentation, including source documents for inspection and copying, in keeping with local regulations. CSL will notify the investigator of any upcoming audit / inspection.

In the event of an audit, all pertinent study-related documentation must be made available to the auditor(s). If an audit or inspection occurs, the investigator at each study site will permit the auditor / inspector direct access to all relevant documents and allocate their time as well as the time of relevant staff to discuss the findings and any relevant issues.

12 Regulatory and Ethics Considerations

12.1 Regulatory Considerations

CSL or its agents will submit the appropriate documents to the local regulatory agencies and, if required by the regulatory agency, wait for approval before proceeding with the clinical investigation.

This study will be conducted under an Investigational New Drug Application, Therapeutic Goods Administration Clinical Trial Notification, or other, as appropriate, and documented in accordance with the applicable regulatory guidelines and requirements.

The procedures set out in this clinical study protocol are designed to ensure that CSL and the investigator abide by the principles of the current ICH GCP guideline on the conduct, evaluation, and documentation of this study, as described in ICH Topic E6 (Guideline for GCP). The study will also be carried out according to all applicable international and national regulatory requirements.

12.2 Institutional Review Board / Independent Ethics Committee

The investigator must submit the clinical study protocol and Informed Consent forms for review by an authorized and properly constituted (according to local guidelines) IRB / IEC. Written approval must be received from the IRB / IEC before commencement of the study.

12.3 Subject Information and Informed Consent

This study involves subjects who cannot be prospectively identified and have life-threatening medical conditions necessitating emergent intervention. Because of the subjects' conditions, the emergent need for intervention, and the limited treatment window during which the IP must be administered for potential efficacy, it is anticipated that obtaining prospective Informed Consent from the subject or their Legally Acceptable Representative may not be possible. For these reasons, the study will be conducted under emergency research Applicable Law which allows subjects to be enrolled into qualifying research without obtaining prospective Informed Consent. However, attempts to collect prospective Informed Consent must be made, if feasible, in accordance with Applicable Laws, and if prospective Informed Consent can be obtained from a subject or their Legally Acceptable Representative prior to enrollment, such Informed Consent must be obtained. Study sites must reference their country-specific Study Consent Manual (where available) for additional requirements. Study sites must follow Applicable Laws in the conduct of the study and should consult their legal

counsel and IRB or IEC for any advice or guidance with respect to any Applicable Laws and IRB or IEC requirements.

If Informed Consent is not obtained from a subject or their Legally Acceptable Representative prior to randomization, Informed Consent for continued participation will be sought after randomization in accordance with the country-specific Study Consent Manual (where available) and where required by Applicable Laws. Similarly, if during the study a subject regains capacity after they are enrolled, Informed Consent for continued participation from the subject shall be sought pursuant to the country-specific Study Consent Manual (where available) and where required by Applicable Laws. Study sites must reference their country-specific Study Consent Manual (where available) for additional requirements. Study sites must follow Applicable Laws in the conduct of the study.

The rationale for emergency research without prospective consent of subjects includes the following general principles:

1. Subjects are in a life-threatening situation, and collection of valid scientific evidence is necessary to determine the safety and effectiveness of the particular intervention.

2. Obtaining Informed Consent is not feasible, because the subject cannot give reasonable consent due to the medical condition and subjects cannot be prospectively selected.

3. There is the prospect of direct benefit to subjects because they are in a life-threatening situation requiring intervention, and risks associated with this study are reasonable compared with standard-of-care therapy alone.

4. The research could not be practically carried out if prospective consent is required.

5. An IRB / IEC has reviewed and approved the Informed Consent procedures and documents to be used with the subjects or their Legally Acceptable Representative for this study.

6. Additional protection of rights will be provided including monitoring of the study by an established IDMC.

Informed Consent may be completed on site or remotely, using paper or electronic means where permitted, in accordance with Applicable Laws. In all cases, the Informed Consent process utilized must follow Applicable Laws and regulatory expectations, including

documentation of the form and process utilized, classification of the signatories, and retention of the signed consent(s). Any reference to "written Informed Consent" in this protocol refers to signatures obtained either on paper or electronically.

If there are any amendments to the clinical study protocol that would directly affect the subject's decision to continue participation in the study (eg, a change in any procedure), the applicable Informed Consent forms must be amended to incorporate the amendment. Subjects or their Legally Acceptable Representative must be informed of the changes promptly in an amended Informed Consent form, prepared for their review and signature.

12.3.1 Consent in the United States

The US FDA and the Department of Health and Human Services outline regulations allowing Exception From Informed Consent (EFIC) for research conducted in an emergency setting. In the US, due to the emergent nature of this study, the study will be conducted with an EFIC. This study qualifies for the EFIC required for emergency research outlined in the US FDA regulation 21 CFR §50.24.

The rationale for EFIC emergency research includes those previously listed in Section 12.3.

Additional protection of rights will be provided, which includes:

1. Community consultation and public disclosure.
2. A subject will only be enrolled without prospective consent if the intervention must be given before consent can be obtained from a Legally Acceptable Representative (hereafter, in the US, Legally Authorized Representative [LAR]).
3. Efforts will be made to inform and honor objections of family members if the LAR is not available (if permitted, according to Applicable Law).

A detailed explanation of each criterion stipulated in the regulations for this exception and how our trial design applies to these criteria is outlined in Appendix 2.

12.4 Subject Confidentiality

All subject names and contact details will be kept Subjects will be identified throughout documentation and evaluation by the number allotted to them during the study. Each subject (and / or their Legally Acceptable Representative, as applicable) will be told that all study findings will be handled in the strictest confidence.

The investigator at the study site will be responsible for retaining sufficient information about each subject (eg, name, address, telephone number and identity in the study) so that regulatory agencies or CSL may access this information should the need arise. These records should be retained in a manner as long as legally mandated according to Applicable Law.

Subject medical records pertaining to the study may be inspected / audited at any time by CSL employees or their duly authorized representatives, a health authority, or the IRB / IEC. All records accessed will be strictly Consent to participate in the study includes consent to these inspections / audits.

12.5 Indemnity and Compensation

CSL has taken out insurance to cover its obligations under both the Indemnity and the Compensation guidelines for injury to subjects involved in the study.

Other details regarding compensation and the obligations of the investigator / CSL are provided in the Clinical Trial Research Agreement for the study (see Section 13.1).

13 Administrative Considerations

13.1 Clinical Trial Research Agreement

This study will be conducted under a Clinical Trial Research Agreement between CSL ("Sponsor") and the institution(s) representing the investigational study site(s) ("Authority"). Financial support to the investigational site(s) will be detailed in the Clinical Trial Research Agreement. The Clinical Trial Research Agreement must be signed before the commencement of the study and will clearly delineate the responsibilities and obligations of the investigator and CSL and will form the contractual basis under which the clinical study will be conducted. Clinical Trial Research Agreements may be executed by electronic signature (current provider DocuSign) in compliance with 21 CFR Part 11 and simple or advanced electronic signature according to European Union Regulation No. 910/2014-eIDAS.

13.2 Clinical Study Registration and Results Disclosure

CSL will provide the relevant clinical study protocol information in public database(s) before or at commencement of the study. CSL may also provide study information for inclusion in national registries according to local regulatory requirements.

Results of this study will be disclosed according to the relevant regulatory requirements. All publications in peer-reviewed medical journals resulting from this study will be listed in the original clinical study protocol registration record.

13.3 Implementation of the Clinical Study Protocol and Amendment(s)

With the exception of medical emergencies, no changes, or deviations in the conduct of the signed clinical study protocol will be permitted without documented approval of CSL's medical monitor or designee and the IRB / IEC. In the event of a medical emergency, the investigator at the study site will institute any medical procedures deemed appropriate. However, all such procedures must be promptly reported to CSL's medical monitor and the IRB / IEC.

Modifications to the clinical study protocol that may affect subject safety or the way the study is to be conducted will be documented in a protocol amendment, which must be approved by the IRB / IEC.

Administrative changes to the clinical study protocol, defined as minor corrections and / or clarifications that have no effect on the way the study is to be conducted, will not require IRB / IEC approval, but will be submitted to the IRB / IEC for their information.

13.4 Protocol Deviations

All instances where the requirements of the clinical study protocol were not complied with will be tracked. Corresponding subjects may be withdrawn from the study at the discretion of the investigator and / or CSL. Clinical study protocol deviations arise when either subjects who have been entered in the study and / or the study sites deviate from the IEC / IRB-approved study protocol.

If a major protocol deviation (ie, a deviation that could have a significant effect on the subject's safety, rights, or welfare and / or on the integrity of the study data) occurs, the investigator must notify CSL and the appropriate IRB / IEC as soon as possible or as per local requirements.

13.5 Documentation and Record Keeping

13.5.1 Data Collection

The investigator (or delegate) will maintain individual records for each subject. These records should include dates when a subject visited the study site, records of vital signs, medical history, administration of IP, any SAEs or AESIs experienced, and other notes as appropriate. These records (electronic or paper) constitute source data.

eCRF entries will be considered source data if the eCRF is the site of the original recordings (ie, there is no other written or electronic record of the data). In this study, the eCRF will not be used as the source document for any data.

An eCRF will be provided by CSL (or delegate) for each randomized (enrolled) subject. The investigator is responsible for ensuring accurate and proper completion of the eCRF in a timely manner so that it always reflects the latest observations on the randomized subjects. All entries on the eCRF must be backed up by source data. All source data will be kept according to all applicable regulatory requirements. Source data must be completed legibly for each randomized subject.

Data from the clinical trial management system and data from the IRT system may be either integrated or later reconciled with the eCRF.

13.5.2 Data Quality Assurance

Data generated throughout the study will be monitored and the eCRFs checked against the subject records for completeness and accuracy. The investigator must provide direct access to source data documents. CSL's study monitor will perform this function.

Following completion of eCRF pages and entry of the data into a database, the data will be checked electronically for consistency and plausibility. Queries will be generated for questionable data and clarification sought from the investigator. These data queries must be resolved in a timely manner by the investigator (or delegate).

13.5.3 Record Retention

The investigator must follow the principles for record retention outlined in the Clinical Trial Research Agreement. An investigator study file prepared by CSL (or delegate), containing all applicable documents for use at the study site, will be made available to the investigator

before the start of the study. All study documentation and materials maintained in the investigator study file must be kept in conformance with applicable national laws and regulations.

All study documentation and materials maintained in the investigator study file at the study site must be available for inspection by CSL's study monitor (or delegate) to determine that all required documentation is present and correct.

The study may be audited or inspected by qualified delegates from CSL or a competent health authority.

Following completion of the study, the investigator is responsible for archiving the investigator's study file, the subject's records and the source data according to applicable regulatory requirements.

13.6 Study and Site Closure

CSL reserves the right to prematurely discontinue or suspend the study either at a particular site or at all study sites at any time and for any reason. If such action is taken, CSL's study monitor (or delegate) will discuss this with the investigator at each study site at that time and notify the investigators in writing. If the study is suspended or terminated for safety reasons, all investigators and the relevant regulatory agencies will be immediately notified of the action as well as the reason for the suspension / termination. The investigator at each study site will advise their IRB / IEC overseeing the study of the suspension / termination.

13.7 Clinical Study Report

A clinical study report will be written after the completion of the study. CSL or its agent will write the report in consultation with the investigator or, if applicable, a nominated coordinating investigator (or delegate). CSL requires that the coordinating investigator will sign the clinical study report.

Progress reports may be provided to the relevant regulatory bodies in accordance with their requirements.

13.8 Use of Data and Publications

The rights and obligations of investigators and CSL concerning any formal presentation or publication of data collected as a direct or indirect result of this study will be addressed specifically in the Clinical Trial Research Agreement for the study.

In addition to maintaining the study websites for the duration and months following study completion (as outlined in the community consultation/public disclosure plan), CSL will also provide study results and links to any scientific manuscripts produced from this study. Advertisements of the study results will also be made, including updates to ClinicalTrials.gov website.

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15 Appendices

Appendix 1 Signature Pages

Signature on Behalf of Sponsor

Study Title: A Prospective, Multicenter, Randomized, Double-Blind, Placebo-Controlled Large Simple Trial Evaluating the Use of BE1116 (4-Factor Prothrombin Complex Concentrate [Kcentra® / Beriplex®]) to Improve Survival in Patients with Traumatic Injury and Acute Major Bleeding

Protocol Number: BE1116_3006

I have read the Clinical Study Protocol Amendment 2 titled "A Prospective, Multicenter, Randomized, Double-Blind, Placebo-Controlled Large Simple Trial Evaluating the Use of BE1116 (4-Factor Prothrombin Complex Concentrate [Kcentra® / Beriplex®]) to Improve Survival in Patients with Traumatic Injury and Acute Major Bleeding" and confirm that, to the best of my knowledge, the protocol accurately describes the design and conduct of the study.

PPD

(Signature)

PPD

Date (DD MMM YYYY)

PPD

(Printed name)

PPD

Signature of the Principal Investigator

Study Title: A Prospective, Multicenter, Randomized, Double-Blind, Placebo-Controlled Large Simple Trial Evaluating the Use of BE1116 (4-Factor Prothrombin Complex Concentrate [Kcentra® / Beriplex®]) to Improve Survival in Patients with Traumatic Injury and Acute Major Bleeding

Protocol Number: BE1116_3006 Site Number:

I have read the Clinical Study Protocol Amendment 2 titled "A Prospective, Multicenter, Randomized, Double-Blind, Placebo-Controlled Large Simple Trial Evaluating the Use of BE1116 (4-Factor Prothrombin Complex Concentrate [Kcentra® / Beriplex®]) to Improve Survival in Patients with Traumatic Injury and Acute Major Bleeding".

By signing this Clinical Study Protocol, I agree to conduct the clinical study, after approval by an Institutional Review Board or Independent Ethics Committee (as appropriate), in accordance with the Clinical Study Protocol, the standards of Good Clinical Practice (as defined by the International Council on Harmonisation) and applicable regulatory requirements.

Changes to the Clinical Study Protocol will only be implemented after written approval is received from CSL Behring (CSL) and the Institutional Review Board or Independent Ethics Committee (as appropriate) with the exception of medical emergencies.

I will ensure that study staff fully understand and follow the Clinical Study Protocol.

_____ _____
(Signature) Date (DD MMM YYYY)

_____
(Printed name)

_____
(Title)

Appendix 2 Exception From Informed Consent for Emergency Research in the United States

This study qualifies under the Exception From Informed Consent (EFIC) requirements for emergency research outlined in 21 CFR §50.24 and all applicable conforming amendments, and shall be conducted in accordance with the provisions contained therein and all other Applicable Laws. Please also refer to the corresponding US Department of Health and Human Services Food and Drug Administration (FDA) *Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors – Exception from Informed Consent Requirements for Emergency Research* [US Department of Health and Human Services, 2013], hereafter EFIC Guidance.

This study qualifies for EFIC because it involves subjects who cannot be prospectively identified and have life-threatening medical conditions necessitating emergent intervention. Because of the subjects' conditions, the emergent need for intervention, and the limited treatment window during which the investigational product must be administered for potential efficacy, it is anticipated that obtaining prospective Informed Consent from subjects or their Legally Acceptable Representatives (hereafter Legally Authorized Representative [LAR]) may not be possible.

In order to provide additional protections for the rights and welfare of subjects, prior to study initiation at a clinical site, community consultation must be performed with representatives of the communities in which the study will be conducted and from which subjects will be drawn, and public disclosure to these communities must occur, each of which must be Institutional Review Board (IRB) reviewed and approved. If a member of the community does not want to participate in the study, there is an option for the subject to receive an "opt-out" bracelet, which, if worn at the time of hospital administration, would exclude the subject from participation in the study. Further details are provided in the Trauma and PCC (TAP) Trial Community Consultation and Public Disclosure Plan. In addition, after the study has concluded or terminated, public disclosure of study results must be provided to the communities and researchers in sufficient detail according to the EFIC Guidance and IRB requirements.

Based on previous data, BE1116 is anticipated to be most effective if administered immediately following injury. In this setting, the patient often has an altered mental status secondary hemorrhagic shock, which can cause confusion and loss of consciousness. As a

result, the patient is often unable to provide consent for study enrollment. LARs are often not immediately available, nor is it typically feasible for the emergency department providers to explain the study and receive consent while caring for the critically injured patient. Taken together, these issues provide sufficient support for EFIC in order to evaluate an intervention that may have significant outcome benefits to this patient population.

In the event that the subject does not survive following the traumatic injury, their information will be included in the data analysis. The deceased's family or LAR will be notified regarding their participation in the study. Due to the severity of the injuries sustained, it is difficult to specify the time frame involved with obtaining the consent, however multiple attempts will be made to obtain consent prior to completion of the study. Each site's consent will be available in English and other appropriate languages based upon the local population. All consenting procedures will be compliant with Health Insurance Portability and Accountability Act and GCP regulations.

One of the key steps for EFIC research is community consultation and public disclosure, a process that connotes consultation between the investigative team, the IRB / IEC, representatives of the communities where the research will be conducted, and communities likely to have the condition. Although traditional methods for community consultation and public disclosure include public meetings and telephone-based surveys, the ability of these modalities to access the target populations, to effectively deliver information, and to elicit useful feedback remains unclear. Investigators within this study team have extensive experience using internet-based social media, as a popular and powerful new modality for communications about EFIC research internationally [Holcomb et al, 2015; Stephens et al, 2013].

Public disclosures will be performed both prior to study enrollment and at the completion of the study in the form of multimedia press releases organized by CSL. Local sites may decide to target notification to specific community groups. These will include plans for the study, including potential risks and benefits, equipoise and a summary of the results of the study upon completion. In the event that the press releases are not widely circulated, advertisements will also be placed on the study website used in the social media campaigns.

Appendix 3 Glasgow Coma Scale

The Glasgow Coma Scale will be used according to the Glasgow structured approach to assessment of the Glasgow Coma Scale. Details are provided at the following location: https://www.glasgowcomascale.org/. A summary of the scoring system is provided below.

Eye Opening

- Spontaneous--open before stimulus: **4 points**
- To sound--after spoken or shouted request: **3 points**
- To pressure—after fingertip stimulus: **2 points**
- None—no opening at any time, no interfering factor: **1 point**
- Non testable (NT)—closed by local factor: NT

Verbal Response

- Orientated—correctly gives name, place and date: **5 points**
- Confused—not orientated but communication coherently: **4 points**
- Words—intelligible single words: **3 points**
- Sounds—only moans / groans: **2 points**
- None—no audible response, no interfering factor: **1 point**
- Non testable (NT)—factor interfering with communication: NT

Best Motor Response

- Obeys commands—obey 2-part request: **6 points**
- Localising—brings hand above clavicle to stimulus on head neck: **5 points**
- Normal flexion—bends arm at elbow rapidly but features not predominantly abnormal: **4 points**
- Abnormal flexion—bends arm at elbow, features clearly predominantly abnormal: **3 points**
- Extension—extends arm at elbow: **2 points**
- None—no movement in arms / legs, no interfering factor: **1 point**
- Non testable (NT)—paralysed or other limiting factor: NT

Appendix 4 Injury Severity Score

The Injury Severity Score (ISS) [Baker et al, 1974; Baker and O'Neill, 1976] will be calculated as follows:

ISS = $A^2 + B^2 + C^2$ where A, B, and C are the Abbreviated Injury Scale (AIS) scores of the 3 most injured body regions. The AIS scores of all 6 assessed body regions will also be recorded.

The AIS incorporates current medical terminology providing an internationally accepted tool for ranking injury severity. The AIS is an anatomically based, consensus-derived, global severity scoring system that classifies an individual injury by body region according to its relative severity on a 6-point scale (1 = minor and 6 = maximal) [AAAM, 2021].

The ISS has a maximum score of 75. Additionally, if any single body system has a score of 6, the ISS score is automatically 75.

The ISS may be calculated after study completion.

Appendix 5 Multiple Organ Failure Assessment

Multiple organ failure will be assessed using the Denver postinjury multiple organ failure score [Sauaia et al, 2009]. The Denver score rates the dysfunction of 4 organ systems (pulmonary, renal, hepatic, and cardiac), which are each graded on a scale from 0 to 3 (see below), with a total score ranging from 0 to 12. Multiple organ failure is defined as a score > 3.

Dysfunction	Grade 0	Grade 1	Grade 2	Grade 3
Pulmonary: PaO_2 / FiO_2 ratio	> 208	208 to 165	164 to 83	< 83
Renal: Creatinine (µmol/L)	< 159	160 to 210	211 to 420	> 420
Hepatic: Total bilirubin (µmol/L)	< 34	34 to 68	69 to 137	> 137
Cardiac: Inotropes	No inotropes	Only one inotrope at a small dose [a]	Any inotrope at a moderate dose or > 1 agent, all at small doses [a]	Any inotrope at a large dose or > 2 agents at moderate doses [a]

FiO_2 = fraction of inspired oxygen; PaO_2 = partial pressure of arterial oxygen

[a] Inotrope doses (in µg/kg/min) are provided in the following summary:

	Small	Moderate	Large
Vasopressin	< 0.03	0.03 to 0.07	> 0.07
Dopamine	< 6	6 to 10	> 10
Dobutamine	< 6	6 to 10	> 10
Epinephrine	< 0.06	0.06 to 0.15	> 0.15
Norepinephrine	< 0.11	0.11 to 0.5	> 0.5
Phenylephrine	< 0.6	0.6 to 3	> 3

Components of the Denver postinjury multiple organ failure score will be collected from medical records, if available, even if all components are not collected per standard of care.

Appendix 6 Charlson Comorbidity Index

Comorbidity will be assessed using the Charlson Comorbidity Index [Quan et al, 2011].

Risk-adjusted hazard ratio for mortality within 1 year after hospital discharge among 55,929 patients aged ≥ 18 years, Calgary, Alberta, Canada, 2004

Variable	Hazard Ratio	Updated Weight	Charlson Weight
Male sex	1.28		
Age ≥ 65 years	4.40		
Charlson comorbidity [a]			
Myocardial infarction	0.99*	0	1
Congestive heart failure	1.91	2	1
Peripheral vascular disease	1.10*	0	1
Cerebrovascular disease	1.10*	0	1
Dementia	2.39	2	1
Chronic pulmonary disease	1.28	1	1
Rheumatologic disease	1.30	1	1
Peptic ulcer disease	1.08*	0	1
Mild liver disease	1.94	2	1
Diabetes without chronic complications	1.12*	0	1
Diabetes with chronic complications	1.22	1	2
Hemiplegia or paraplegia	2.26	2	2
Renal disease	1.43	1	2
Any malignancy, including leukemia and lymphoma	2.28	2	2
Moderate or severe liver disease	3.83	4	3
Metastatic solid tumor	6.01	6	6
AIDS/HIV	3.69	4	6
Maximum comorbidity score		24	29

AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus

* $P > 0.05$.

[a] The following comorbid conditions were mutually exclusive: diabetes with chronic complications and diabetes without chronic complications; mild liver disease and moderate or severe liver disease; and any malignancy and metastatic solid tumor.

Source: Table 2 in [Quan et al, 2011].

Appendix 7 Berlin Criteria for ARDS

Acute respiratory distress syndrome (ARDS) will be assessed using the Berlin criteria [ARDS Definition Task Force, 2012; Fan et al, 2018; Matthay et al, 2021].

The expanded Berlin definition of acute respiratory distress syndrome

	Acute Respiratory Distress Syndrome
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging [a]	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation [b]	
Mild	200 mm Hg < PaO_2/FiO_2 ≤ 300 mm Hg with PEEP or CPAP ≥ 5 cm H_2O [c]
Moderate	100 mm Hg < PaO_2/FiO_2 ≤ 200 mm Hg with PEEP ≥ 5 cm H_2O
Severe	PaO_2/FiO_2 ≤ 100 mm Hg with PEEP ≥ 5 cm H_2O
High-flow nasal oxygen	Use of high-flow nasal oxygen ≥ 30 L/min

CPAP = continuous positive airway pressure; FiO_2 = fraction of inspired oxygen; PaO_2 = partial pressure of arterial oxygen; PEEP = positive end-expiratory pressure.

[a] Chest radiograph or computed tomography scan.

[b] If altitude is higher than 1000 m, the correction factor should be calculated as follows: [PaO_2/FiO_2 × (barometric pressure/760)].

[c] This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

Source: Table 3 in [ARDS Definition Task Force, 2012]; [Matthay et al, 2021].

Components of the Berlin Criteria for ARDS will be collected from medical records, if available, even if all components are not collected per standard of care.

Appendix 8 Defined Terms

Informed Consent means the process by which a subject or their Legally Acceptable Representative voluntarily confirms his or her willingness to participate in a particular trial after having been informed about all aspects relevant to the subject's decision to participate. Informed Consent is documented by means of a written (whether electronic or paper copy), signed and dated Informed Consent form. For the avoidance of doubt, this definition of Informed Consent includes assent of a minor subject along with corresponding Informed Consent of their Legally Acceptable Representative, when allowed by Applicable Law. Informed Consent nuances, processes, and requirements are further discussed in the applicable country-specific Study Consent Manual (where available).

Legally Acceptable Representative means an individual or judicial or other body authorized under Applicable Law to provide Informed Consent on behalf of a prospective subject, to the subject's participation in the clinical trial. The term Legally Acceptable Representative may be referred to by an alternative defined term (eg, Legally Authorized Representative in the US) in the applicable country-specific Study Consent Manual (where available) according to the nomenclature used in the applicable country.

Applicable Law(s) means all applicable laws, rules, regulations, guidance, regulatory and IRB / IEC requirements related to the conduct of the study and emergency research.

Signature Page

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