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SIV Slides for Physician determining eligibility

11 Jul 2023

Version 1.0

TAP

TRAUMA AND PCC STUDY

Protocol Overview

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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

- Trial is expected to be conducted over 3 years. The FPI was on 28 March 2023. So, plan to end the trial in 3Q2026.

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Design:

Phase 3

Large, Simple Trial

Pragmatic

Randomized

Double-blind

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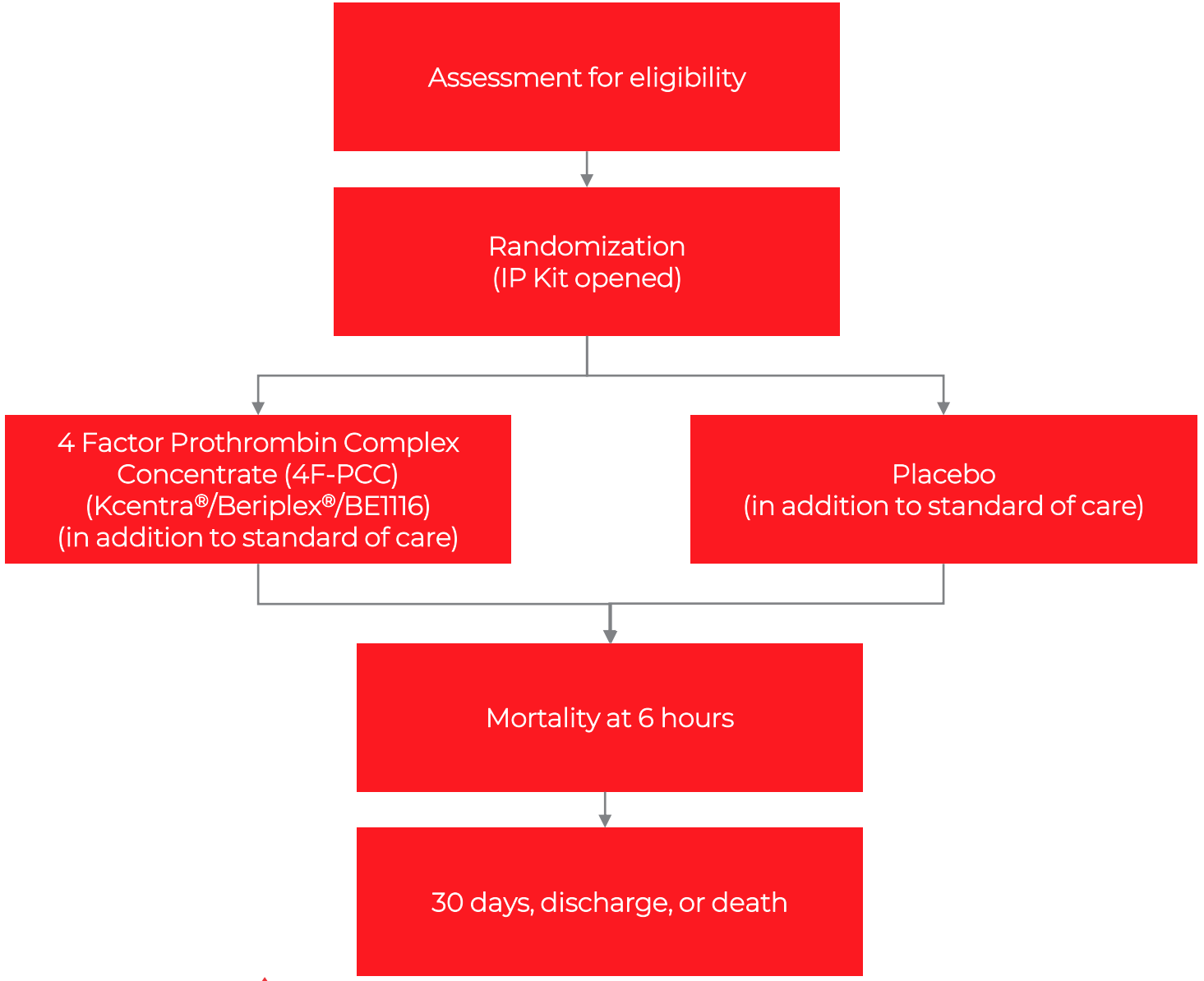
Enrollment

Allocation

Follow-Up (Primary Endpoint)

Follow-Up (Secondary Endpoints)



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Standard of Care:

Level I or II trauma center (or equivalent)

Massive transfusion/hemorrhage protocol

(Initial) ratio-guided transfusion or whole blood

Approximately 120 sites worldwide

Up to 8000 patients

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Intervention:

Single dose of IP (4F-PCC or Placebo)

Must be started with 90 minutes of patient's arrival to hospital

Based on weight (estimated or measured)

≥ 50 to <75 kg (165 lbs): 2000 IU

≥ 75 kg (165 lbs): 3000 IU

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Time = 0 at randomization, when study kit is opened.

Time of study kit opening must be recorded on the IP administration form.

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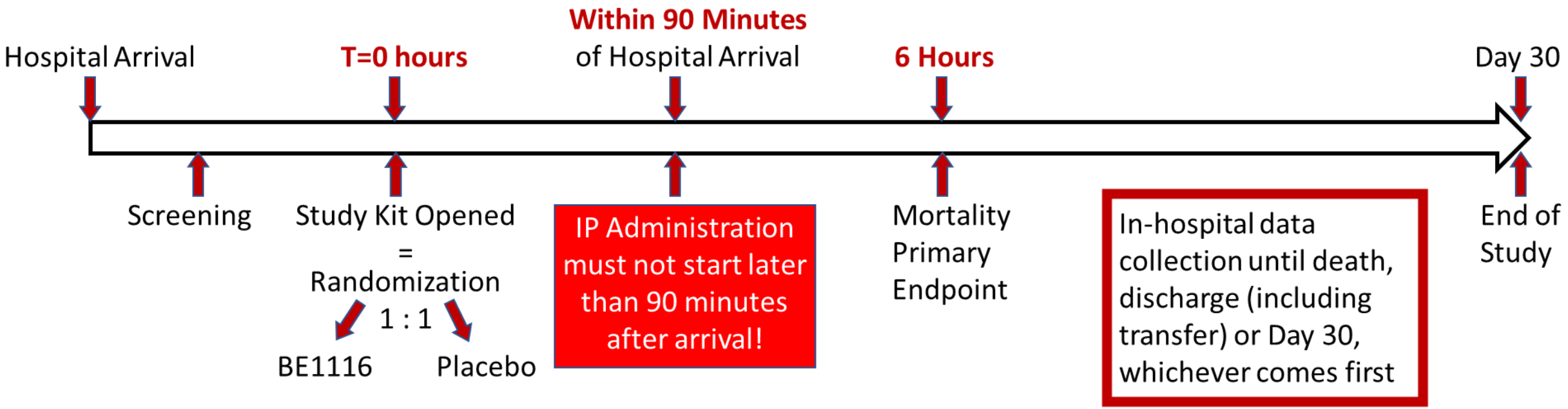
TAP Trial Schematic



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Primary Endpoint:

- all cause mortality at 6 hours after randomization

Secondary Endpoints:

- All-cause in-hospital mortality up to 24 hours after randomization
- All-cause in-hospital mortality up to 30 days after randomization
- Surgical or interventional radiological procedures to stop bleeding related to the primary injury up to 24 hours after randomization

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Secondary Endpoints (cont'd):

- Serious Adverse Events (SAEs) considered related to IP
- Adverse events of special interest (AESIs):
  - Thromboembolic events (TEEs), symptomatic or asymptomatic, and arterial or venous (e.g., deep vein thrombosis, pulmonary embolism, ischemic stroke, myocardial infarction)
  - Acute respiratory distress syndrome (ARDS)
  - Multiple organ failure
  - Acute kidney injury (AKI) requiring renal replacement therapy (dialysis, hemofiltration, or hemodiafiltration)

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Inclusion Criteria

1.A1. (a) Estimated or actual age ≥15 years

FOR UK: Estimated or Actual Age ≥ 16 years

FOR AUS: 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 OR

(b) Revised Assessment of Bleeding and Transfusion (RABT) Score ≥2

4. Activation of massive transfusion/hemorrhage protocol

5. At least 1 unit of blood/product spiked (transfusion bag connected to an IV fluid line and ready to start)

6.A1. Anticipated start of IP infusion within 90 minutes of arrival in hospital

Exclusion Criteria

1.A1. Cardiopulmonary resuscitation for ≥5 **consecutive** minutes
2. Isolated penetrating or blunt cranial injury
3. Known anticoagulation treatment or a history of TEE (past 3 months)
4.A1. Isolated burns estimated to be ≥20% TBSA or 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 significant increase prothrombotic risk (AT-III deficiency, Factor V Leiden, etc.)
10. Known or suspected pregnancy
11. Known anaphylactic or severe systemic reactions to BE1116 or components
12. Prisoner
13. Known “Do Not Resuscitate” order
14. Subject or a family member voiced an objection to participation in the trial or were wearing an “opt out” bracelet
15.A1. Known participation in another interventional clinical study, unless agreed
16.A1. Known treatment with prohibited medications (3F-PCC, 4F-PCC, aPCC/FEIBA, rFVIIa) after trauma and before randomization

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Prohibited Medications/Therapies

Medication / Therapy	Dose	Prohibited Period of Use
3F-PCC	Any	From trauma through 24 hours after randomization
4F-PCC	Any	From trauma through 24 hours after randomization
aPCC (FEIBA)	Any	From trauma through 24 hours after randomization
Factor VIIa	Any	From trauma through 24 hours after randomization

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Study Procedures after enrollment

- Administration of study IP
- Timely reporting of any SAEs and AESIs (i.e. within 24 hours of site/investigator awareness)

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Adverse Events

- An Adverse Event or experience (AE) is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.
- An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- IMPORTANT: Non-serious AEs (except AESIs) will not be recorded in this study.
- Adverse Events do not include
  - Medical or surgical procedures. The condition that leads to the procedure is the AE/SAE
  - Overdoses of study product or concomitant medication that do not result in any sign or symptom

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Serious Adverse Events

- A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose
  - is (immediately) **life-threatening**
  - requires in patient **hospitalisation** or prolongation of existing hospitalisation (>24 hours)
  - results in permanent or significant **disability or incapacity**
  - is a congenital anomaly or **birth defect**
  - is otherwise a **significant medical event**
  - results in **death**

Deaths due to the following will NOT be considered an SAE and will only be captured on the death page of the eCRF:

- Hemorrhagic shock or exsanguination;
- Traumatic brain injury; pulmonary contusion; and
- Tension pneumothorax.

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Adverse Events of Special Interest:

- Thromboembolic Events (TEEs)
  - Kcentra®/Beriplex® contains clotting factors
  - No significant risk seen with prior studies and experience
- Complications of Trauma
  - Acute Respiratory Distress Syndrome
  - Multiple Organ Failure
  - Acute Kidney Injury requiring renal replacement therapy

Only SAEs and AESIs will be collected

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Observation Period

- The observation period for SAE /AESI reporting for an individual subject will start at the time of randomization for participation in the study through to the In-hospital Follow-up Period (up to the time of death/hospital discharge/Day 30, whichever occurs first).
- If an SAE occurs at any time after the observation period has finished and there is at least a possible causal relationship to the investigational product (IP), the event must be reported to CSL.
- The investigator/site must notify CSL Pharmacovigilance within 5 calendar days of becoming aware of a Pregnancy.

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Breaking the Blind for an Emergency

- In rare emergency situations (warfarin) for subject safety, an investigator may unblind the randomization code for an individual subject if knowing the treatment assignment will change subject management.
- Whenever possible, the investigator should consult with CSL Medical Monitor before unblinding the randomization code.
- Reason for unblinding must be documented in the subject's source documents.
- The Suvoda IRT system is used to unblind. The steps to manage the unblinding in the IRT system will be discussed in more detail during the IRT discussion.

Emergency Unblinding Scenario

- Patient enrolled in TAP and IP administered.
- Family member arrives 1 hour later and informs hospital that patient is taking warfarin (coumadin) daily
- Urgent warfarin reversal is indicated.
- PI should unblind without contacting CSL to determine whether or not reversal with active IP (Kcentra®/Beriplex®)already happened.
- If patient received placebo, it is safe to treat as per your site's SOC (may include PCCs)
- If patient received Kcentra®/Beriplex®, treat as per your site's SOC

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Pregnancy and Women of childbearing potential

- Known pregnant patients are excluded from this study
- Pregnancy test may be done on women of child-bearing potential as per your institution's normal standard of care

    - If a subject is discovered to be pregnant prior to IP administration – do not administer IP, subject will remain in the study if the study IP kit has been opened (randomized)
    - If a subject is discovered to be pregnant during IP administration – stop the administration of IP, subject will remain in the study
        - Follow up outcome of the pregnancy, as feasible (if permitted by subject)
    - If a subject is discovered to be pregnant after IP administration, the subject will remain in the study
        - Follow up outcome of the pregnancy, as feasible (if permitted by subject).

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Consent Process Overview – United States

- This trial is performed under Exception-From-Informed-Consent (EFIC) regulations
- The FDA does require a prospective (informed) consent pathway, in the unlikely event that this is deemed feasible
- Given the clinical setting and urgency, most (possibly all) subjects will not have capacity to provide informed consent
- Similarly, prospective (informed) consent by Legally Authorized Representatives (LARs) will usually not be feasible
- Consent (from LARs and/or patients) for continued participation must be sought as soon as practical

Consent Process Overview – United Kingdom

- This trial is performed under Research-Without-Consent regulations
- Given the clinical setting and urgency, most (possibly all) subjects will not be able to provide informed consent
- If consent could be obtained prior to enrollment, do not enroll subject until prospective consent process is approved at site.
- Similarly, prospective (informed) consent by Personal or Professional Legal Representatives will usually not be reasonably practicable.
- If it is reasonably practicable to obtain informed consent from legal representative prior to enrollment of subject, do not enroll subject until prospective consent process is approved at site.

Consent for Continued Participation – United Kingdom

- Consent (from representatives and/or patients) for continued participation must be sought as soon as practical
- When possible, the patient's GP will be notified by letter that the patient was enrolled into the TAP study (letter on Longboat)

Summary:

Straight-up comparison (4F-PCC vs placebo)

Second-largest interventional trauma trial

Contemporary outcomes

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Investigator Brochure

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Kcentra®/Beriplex®
(4 Factor-Prothrombin Complex Concentrate; 4F-PCC)

- Derived from pooled human plasma.
  - Each donor tested negative for HBsAg, HIV, HCV, HAV.
  - Pooled plasma is also tested for parvovirus B19.
  - Highly purified, heat-treated, virus-filtered, lyophilized.
- Blood coagulation factor replacement product (Factors II, VII, IX, X, Protein C, Protein S).

- 4 Factors
- Dosed by factor IX

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Kcentra®/Beriplex® (4F-PCC) Current Use

- Current indication in USA: Urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonists (e.g. warfarin) therapy in adult patients with acute major bleeding or need for urgent surgery/invasive procedure

- Dosing is weight and INR dependent.

Table 1: Dosage Required for Reversal of VKA Anticoagulation in Patients with acute major bleeding or need for an urgent surgery/invasive procedure

Pre-treatment INR	2–< 4	4–6	> 6
Dose* of Kcentra (units† of Factor IX) / kg body weight	25	35	50
Maximum dose‡ (units of Factor IX)	Not to exceed 2500	Not to exceed 3500	Not to exceed 5000

* Dosing is based on body weight. Dose based on actual potency is stated on the vial, which will vary from 20-31 Factor IX units/mL after reconstitution. The actual potency for 500 unit vial ranges from 400-620 units/vial. The actual potency for 1000 unit vial ranges from 800-1240 units/vial.

† Units refer to International Units.

‡ Dose is based on body weight up to but not exceeding 100 kg. For patients weighing more than 100 kg, maximum dose should not be exceeded.

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Beriplex®

- Current EU indications:
  - Treatment of bleeding and perioperative prophylaxis of bleeding in acquired deficiency of the prothrombin complex coagulation factors, such as deficiency caused by treatment with vitamin K antagonists, or in case of overdose of vitamin K antagonists, when rapid correction of the deficiency is required
  - Treatment of bleeding and perioperative prophylaxis in congenital deficiency of any of the vitamin K dependent coagulation factors when purified specific coagulation factor product is not available.

Pre-treatment INR*	2.0 – 3.9	4.0 – 6.0	> 6.0
Approximate dose mL/kg b.w. †	1	1.4	2
Approximate dose IU (Factor IX)/kg b.w.	25	35	50

* INR = [prothrombin time of patient's sample / prothrombin time of control plasma]^{ISI}. The results are used to calculate the relative sensitivity of the sample compared with the WHO standard International Sensitivity Index (ISI).

† Dose based on actual potency stated on the vial, which vary from 20-31 Factor IX IU/mL after reconstitution.

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Kcentra®/Beriplex® (4F-PCC) Contents and Administration

Active ingredients	
FII (IU/mL)	19 - 40
FVII (IU/mL)	10 - 25
FIX (IU/mL)	20 - 31
FX (IU/mL)	25 - 51
PS (IU/mL)	12 - 34
PC (IU/mL)	21 - 41
Other ingredients	
PZ (IU/mL)	51.3
Excipient concentrations	
ATIII	0.2 – 1.5
Heparin (IU/mL)	0.4 - 2
Sodium citrate	40 – 80 mg
Sodium chlorate	60 – 120 mg
Albumin	40 – 80 mg
Purity (% total protein)	42%
Thrombin inhibitory capacity	66 IU/mL
Activated factors (naPTT)	Negative
Virus inactivation process	Pasteurization, Nanofiltration

Clinical properties	
Administration route	Intravenous
Infusion rate	Max. 8.4 mL/min
PK	FIX $t_{1/2}$: mean 42.4 h
Clinical studies	VKA reversal
Warnings and precautions	Transmissible infectious agents
	Increased risk of DIC and TEEs
	Hypersensitivity to heparin (HIT)
	Allergic, anaphylactic reactions

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Safety of Kcentra®/Beriplex® (4F-PCC)

- No thrombotic risks in rat and rabbit trauma model systems.
- Porcine trauma model using dose of 50 IU/kg dose showed
  - Thrombi with DIC-like syndrome
  - Improved survival
- Ten interventional and 2 post-marketing studies show no increase in thromboembolic events (TEE)
- Post-marketing study shows no increased risk of thrombosis
  - 20 years of post-marketing experience supports safety.
- Evidence to date suggests that there likely will be no increased thrombotic risk in trauma patients

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Training, Delegation and ICH GCP Documentation Practices

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Investigator Responsibilities – Good Documentation

Source Documents

- Maintain adequate and accurate source documents and trial records

- ALCOA-C: Source data should be
  - Attributable: who wrote it?
  - Legible: Can you read it?
  - Contemporaneous: Written in a timely manner
  - Original: Not a copy
  - Accurate: Consistent with other source
  - Complete: Contains all information

- Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary

- Record Retention – should be documented in the Clinical Trial Agreement

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Site Signature and Delegation of Responsibilities Log

This log documents the tasks for which you are responsible.

- Review Inclusion/exclusion Criteria
- Determine eligibility

Training pertaining to this study will be documented on the Site Training Log.

CSL	Site Signature and Delegation of Responsibilities Log
Protocol Number: BE1116_3006	**Site Number:** <<>>
Protocol 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	**Principal Investigator Name:**

Name	Signature	Initials	Study Role	Key Study Task(s) (choose from list below)	Start (dd/mmm/yyyy)	End (dd/mmm/yyyy) (complete only if prior to end of study)	PI Initials & Date (dd/mmm/yyyy)

Consent/Assents

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Trial is using Exception from Informed Consent (EFIC)

There was public disclosure and community consultation about this study because patients must be quickly enrolled during an emergency.

Community members had opportunity to ask questions, voice opinions, and opt-out by requesting and wearing an opt-out bracelet.

- Do not enroll a patient wearing this bracelet.

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Trial is using Exception from Informed Consent (EFIC)

Prospective informed consent from the patient or their legally authorized representative (LAR*) is required only if feasible. This is because:

- Patients who meet the inclusion criteria for the TAP trial will rarely have capacity to provide prospective, informed consent
- The consenting process could interfere with emergency treatment or delay care. This should never happen. It is not ethical.
- In most cases there will not be time to obtain informed from LARs
  - Patient or LAR should only be approached for consent after the medical team has discussed patient's condition with them, making it even harder to obtain prospective informed consent.

**An LAR is defined by your local regulations (state/district) and may be court appointed. Usually, they are the closest adult relative.*

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Consent in Exception from Informed Consent (EFIC)

- FDA requires researchers to seek prospective consent of patient if feasible.
  - If not feasible, prospective consent of legally authorized representative (LAR) must be sought if feasible
  - In prior similar trials with similar entry criteria, very few if any patients or their LARs provided prospective informed consent
- If prospective consent is not feasible, then patient can still be enrolled
  - Consent for continued participation following enrollment must be sought from surviving patient or their LAR

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United Kingdom

- Will not enroll subjects < 16 years old
  - Age of majority is 16 in the UK.
  - If an adolescent < 16 years old is enrolled, seek consent from parent/guardians and seek assent from adolescent subject once they have recovered enough to have an age appropriate understanding of the study.

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Consent to Continue Process - UK

- No prospective informed consent will be sought in the UK yet, only consent for continued participation.
- If consent could be obtained prior to enrollment from subject, do not enroll subject until prospective consent process is approved at site.
- A subject, subject's personal legal representative, or a professional legal representative may consent for continued participation
- Personal legal representative: individual or judicial or other body authorised under the applicable law to provide consent on behalf of a subject, to the subject's participation in the procedures involved in the research

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